AF/1646/18 ZIW

In the United States Patent and Trademark Office Board of Patent Appeals and Interferences (37 CFR 1.191)

In re application of: James P. Elia

Docket No.: 1000-10-CO1

Serial No. 09/836,750

Group No.: 1646

Filed: February 27, 2001

Examiner: Elizabeth C. Kemmerer, Ph.D.

For: METHOD FOR GROWING MUSCLE IN A HUMAN HEART

MAIL STOP APPEAL BRIEF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Appellant hereby submits an Appeal Brief, in triplicate, in furtherance of the Notice of Appeal mailed on April 7, 2005, and received by the Patent and Trademark Office on April 14, 2005, in the above-identified application.

The item(s) checked below are appropriate:

1. **Status of Applicant/Appellant**
   This application is on behalf of
   ☒ a small entity

2. **Fee for Filing Appeal Brief**
   Pursuant to 37 CFR 1.17(f) the fee for filing the Appeal Brief is:
   ☒ a small entity — Appeal Brief fee due: $ 250.00

3. **Extension of Term**
   a) ☐ Extension requested:

Extension (months)	Fee for small entity
one month	$ 60.00
two months	$ 225.00
three months	$ 510.00
four months	$ 795.00
five months	$1,080.00

☐ Request Extension for ______ months

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3. **Extension of Term *(continued)***

Or

b) X No Extension requested

4. **Total Fee Due**
X The total fee due is:

X Appeal Brief fee $250.00

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Total Fee Due: $ 250.00

5. **Fee Payment**
X Attached is Check No. 903 in the sum of $ 250.00

Date: June 9, 2005

Reg. No.: 26,611

Gerald K. White
Signature of attorney

Gerald K. White
Type or print name of attorney

CERTIFICATE OF MAILING

I hereby certify that the attached APPELLANT'S APPEAL BRIEF was deposited, in triplicate, as First Class Mail, in an envelope addressed to Mail Stop APPEAL BRIEF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 this 9th day of June, 2005.

Dated: June 9, 2005

Gerald K. White

Printed Name: GERALD K. WHITE

GERALD K. WHITE & ASSOCIATES, P.C.
205 W. Randolph Street, Suite 835
Chicago, IL 60606
Phone: (312) 920-0588
Fax: (312) 920-0580
Email: gkwpatlaw@aol.com

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BOARD OF PATENT APPEALS AND INTERFERENCES

In Re Application of: James P. Elia	)	Docket No.: 1000-10-CO1
	)	
Serial No.: 09/836,750	)	Group Art Unit: 1646
	)	
Filed: April 17, 2001	)	
	)	Examiner: Elizabeth C. Kemmerer, Ph.D.
For: METHOD FOR GROWING MUSCLE IN A HUMAN HEART	)	
	)	

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APPELLANT'S APPEAL BRIEF

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Phone: (312) 920-0588
Fax: (312) 920-0580
Email: gkwpatlaw@aol.com

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REAL PARTIES IN INTEREST

The real parties in interest in the instant appeal are Assignees, Dental Marketing Specialists, Inc., an Arizona corporation, 9377 E. Bell Road, Suite 385 Scottsdale, Arizona 85260, and Jerry W. Bains and Salee C. Bains Irrevocable Trust, 9013 Red Lawrence Drive, Carefree, Arizona 85377. Subsequent to the assignment recordal for the instant application, the address of Dental Marketing Specialists, Inc., changed to 7364 East Crimson Sky Trail, Scottsdale, Arizona 85262. Also subsequent to the assignment recordal for the instant application, the address of Jerry W. Bains and Salee C. Bains Irrevocable Trust, changed to 39096 N. 102nd Way, Scottsdale, Arizona 85262.

RELATED APPEALS AND INTERFERENCES

There are two related appeals known to Applicant, Appellants' legal representative, or Assignee, which may directly affect or be directly affected by or may have a bearing on the Board's decision in the pending appeal.

First, an appeal from the Final Rejection of June 1, 2004, in patent application Serial No. 09/794,456 was filed on November 23, 2004; and an Appeal Brief was filed on March 25, 2005.

Second, an appeal from the Final Rejection of October 18, 2004, in patent application Serial No. 09/064,000 was filed on January 18, 2005, and an Appeal Brief was filed on April 12, 2005.

The instant application and patent application Serial No. 09/794,456 are continuations of Serial No. 09/064,000.

There are no related interferences known to Applicant, Appellants' legal representative, or Assignee, which will directly affect or be directly affected by or having a bearing on the Board's decision in the pending appeal.

STATUS OF CLAIMS

Claims 1-5, 204, 205, and 237 are cancelled.

Claims 236, 238, 239, 243-253, and 256 are pending, stand finally rejected, and are included in the instant appeal. Appellant notes that claims 238, 239, and 243 are dependent upon cancelled claim 237. When claim 237 was cancelled, Appellant inadvertently failed to change the dependency of claims 238, 239, and 243 to depend upon claim 236, rather than upon cancelled claim 237. Claim 237 previously depended upon claim 236. Neither the Examiner nor Appellant noticed this error prior to filing of the instant Brief. Appellant will make the correction of such dependency at an appropriate time. The Board is respectfully requested, for purposes of this Appeal only, to treat the dependency of claims 238, 239, and 243 as though such claims depended upon claim 236 because such error is one of obvious omission and is editorial in nature. Such error is regretted.

Claims 6-203, 206-235, and 240-242 are withdrawn from consideration as drawn to a non-elected invention.

The subject matter described in claims 254 and 255 has been withdrawn from appeal.

STATUS OF AMENDMENTS

No amendment has been made or entered subsequent to the Final Rejection of December 12, 2004.

SUMMARY OF INVENTION

Appellant's invention is directed to a method of using a novel combination of old and well-known compositions (materials), old and well-known administration techniques, and old and well-known medical apparatus to produce a novel result, i.e., the growth of new cardiac muscle and a new artery. Antecedent basis in the specification for various claim elements is included below.

Appellant's novel contribution to the medical art is defined in the broadest scope in generic claim 236 on appeal as comprising a method for growing a new portion of a pre-existing heart by placing a growth factor in a body of a human patient and growing new cardiac muscle and growing a new artery in said heart (page 45, lines 17-23; page 46, lines 3-16). A growth factor, as called for by claim 236, broadly encompasses compositions and living organisms, which promote the growth of soft tissue in the body of a patient (page 20, lines 10-14). Claims 238 and 239, which depend on claim 236, describe repairing a dead portion (claim 238) or a damaged portion (claim 239) of a pre-existing heart (page 45, lines 17-23; page 46, lines 3-16). Appellant's invention specifically describes using patient size, vascularity, simplicity of access, ease of exploitation, or any other desired factors in determining the selected area of the patient for administering said growth factor (page 45, lines 1-4). Appellant describes monitoring heart repair by determining blood flow through new arteries by using any readily available commercial device such as ultrasound, angiogram, etc. (page 56, lines 20-25).

Appellant's elected invention is defined in claim 243, which directly depends from claim 236, and specifically limits the growth factor to a subgenus comprising a member selected from the group consisting of cells, cellular products, and derivatives of cellular products (page 37, lines 19-26). Claim 244 further limits the invention by specifying that the growth factor of claim

243, comprises a cell (page 37, lines 19-26); claim 245 further defines the growth factor of claim 244 as a multifactorial and non-specific cell (page 21, lines 14-15; page 37, lines 19-21; and page 50, lines 2-5); and claim 246 further defines the multifactorial and non-specific cell of claim 245 as comprising a stem cell (page 37, lines 19-21). Claim 247 directly depends from claim 236 and further limits the method of said claim 236 by reciting that the growth factor is placed in said patient by injection (page 21, line 5; page 45, lines 13 and 14); claim 248 directly depends from claim 247 and defines said injection as being intravenous (page 45, line 14); claim 249 directly depends from claim 247 and defines the injection as being intraluminal (page 45, line 14); and claim 250 directly depends from claim 247 and defines the injection as being intramuscular (page 45, lines 1-3). Claim 251 depends from and further limits the method of claim 236 by requiring the growth factor be placed in said patient by a carrier (page 21, lines 3-6); and claim 252 depends from and requires that the carrier of claim 251 comprise an angioplasty balloon (page 45, line 15). Claim 253 depends from claim 236 and defines the growth factor as comprising a gene and a cell (page 46, lines 3-16). Claim 256 describes growing a new portion of a pre-existing heart comprising placing a stem cell in a body of a patient to grow new cardiac muscle (page 45, lines 17-23; page 46, lines 3-16). Claim 256 is broader in some respects and more narrow in other respects than above-mentioned claim 236.

ISSUES

1. Whether the Examiner's rejection of claim 254 (Appellant assumes Examiner intended to reject claim 245) for failure to comply with the definiteness requirement of 35 U.S.C. §112, second paragraph, constitutes reversible error.

2. Whether the Examiner's rejection of claims 248, 249, and 252 for failure to comply with the written description requirement of 35 U.S.C. §112, first paragraph, constitutes reversible error.

3. Whether the Examiner's rejection of claims 248 and 249 for failure to comply with the enablement requirement of 35 U.S.C. §112, first paragraph, constitutes reversible error.

4. Whether the Examiner's rejection of claims 236, 238, 239, 243-253, and 256 for failure to comply with the enablement requirement of 35 U.S.C. §112, first paragraph, constitutes reversible error.

GROUPING OF CLAIMS

Each ground of rejection set forth in the Final Rejection involves a group of two or more claims, except for the rejection of claim 254 (Appellant assumes Examiner intended to reject claim 245) under 35 U.S.C. §112, second paragraph.

Claims 248 and 249, as well as the group of claims comprising 236, 238, 239, 243-253, and 256, all of which stand rejected under 35 U.S.C. §112, first paragraph, do not stand or fall together, and Appellant provides further explanation below why such claims are separately patentable.

Appellant specifically points out that the Examiner has not treated the claims separately in the various rejections at issue. Exemplary of this situation is the rejection of claims 248 and 249 under the first paragraph of 35 U.S.C. §112, where the Examiner basically only discussed enablement of intravenous administration. Appellant believes that each type of administration should be considered separately. In addition, the group of claims comprising 236, 238, 239, 243-253, and 256, have been rejected for lack of enablement, whether or not they are drawn to: 1) growing new cardiac muscle and a new artery in the heart; 2) growing new cardiac muscle; 3) repairing a dead portion of the heart; 4) repairing a damaged portion of the heart; 5) the use of multifactorial and non-specific cells; 6) the use of a stem cell; 7) the use of intramuscular injection; or 8) the use of a gene and a cell. It was error on the part of the Examiner not to address each of the specific claim limitations mentioned above. Appellant believes that each of such limitations must be considered separately.

ARGUMENT

In an attempt to conserve the readers' time but yet fully explain Appellant's position, this Brief is reorganized from the pattern set by the Examiner during prosecution. By including claims 248 and 249 in both rejections under 35 U.S.C. §112, first paragraph, for lack of enablement, the Examiner has added to the complexity and length of Appellant's Brief. Also contributing to the complexity and length of Appellant's Brief is the Examiner's erroneous reading of the claims as containing subject matter not set forth in the claims.

Rejection of Claim 254 Under 35 U.S.C. §112, second paragraph

Claim 254 stands finally rejected for failure to satisfy the definiteness requirement of 35 U.S.C. §112, second paragraph. Appellant believes that the Examiner intended to reject claim 245, rather than claim 254, because claim 245 contains the questioned language. Appellant, accordingly, has directed his remarks to claim 245. Specifically, the Examiner considered the "multifactorial and non-specific" language to be indefinite. Appellant respectfully disagrees.

Page 37, line 19 of Appellant's specification defines "multifactorial and non-specific cells" as stem cells and germinal cells. Page 48, lines 13-15, discloses that, "if germinal cells (and in some cases, stem cells) are utilized a direct differentiation and morphogenesis into an organ can occur...". In addition, page 50, lines 2-5 define "multifactorial and non-specific" growth factors as being "pluripotent." Appellant believes that one skilled in the medical art, based upon the above portions of the specification, would understand the meaning and intended scope of "multifactorial and non-specific."

On page 20 of the Final Rejection, referring to the disclosure at page 37, line 19, the Examiner stated that, "While this sentence provides examples of what the term encompasses, it

does not provide an unambiguous definition." However, the Examiner failed to specifically identify why one skilled in the art would find Appellant's disclosure ambiguous. An applicant is not required to provide a definition for terms that are well known by those skilled in the art.

On October 21, 2004, prior to the date of the Final Rejection, Appellant submitted a Fifth Supplemental Information Disclosure Statement (hereinafter "5th IDS") to provide a dictionary definition of the terms "multifactorial and non-specific." The Examiner acknowledged receipt of the 5th IDS (Final Rejection, page 2) but did not explain in the Final Rejection wherein the dictionary definition failed to support Appellant's position that one skilled in the art would understand the meaning of the questioned language. The 5th IDS contains the following definitions:

> "Multifactorial" means: "involving or depending on several factors or causes (especially pertaining to a condition or disease resulting from the interaction of many genes)".
>
> "Nonspecific" means: "...undestined, undetermined, undifferentiated,..."

It is clear from a reading of Appellant's specification that the qualities and characteristics of multifactorial and non-specific cells can be found in cells such as: stem cells, germinal cells, and pluripotent cells. No one skilled in the art would seriously question that a fundamental property of all of these cells is that they are undifferentiated. Also, no one skilled in the art would question that "pluripotent" cells are undifferentiated stem cells, which are highly versatile (multifactorial) and can give rise to the growth of multiple tissues, i.e., endoderm, mesoderm, and ectoderm. Appellant recognized that such versatility results from a uniquely unspecialized condition, which allows such cells to be used to carry out the non-specific tissue function

disclosed and claimed in the subject application for growing new cardiac muscle and a new artery in a heart.

During the prosecution of this application – unlike in the prosecution of related application Serial No. 09/794,456, concurrently on appeal – the Examiner made no mention of conducting a search to determine the meaning of the criticized language and did not mention that the terms could not be found. As Appellant indicated in the Appeal Brief for application Serial No. 09/794,456, a cursory search for the term "stem cell" via the Internet search engine, Google, revealed the well-known medical fact that stem cells have the potential to differentiate into every cell type, and it is the versatility and non-specifically of these cells that give them therapeutic application.[1] Such search result further confirms that one skilled in the art to which the invention pertains would understand the criticized terminology.

The purpose of the second paragraph of 35 U.S.C. §112 is to ensure due process of law, i.e., to give notice to the public as to the metes and boundaries of protection adhering to patent claims. In re Hammack, 427 F.2d 1378, 166 USPQ 204 (CCPA 1970). The Examiner, in the Final Rejection, has questioned the meaning of Appellant's terminology "cascade of genetic material" found on page 37, lines 19-21, of the specification and stated that such language "makes no sense." Such question is irrelevant to the instant definiteness rejection because the questioned language does not appear in the claims. Even though this terminology may not be familiar to the Examiner, the questioned terminology is commonly employed in the medical art and is well understood by those skilled in the art. Note that use of the questioned terminology may be found in an article published in 2001 by the American Heart Association, entitled "Tubes, Branches, and Pillars," authored by Hellmut G. Augustin, and attached hereto as Exhibit

[1] http:// www.meta-library.net/bioglosss/stemcel-body.htm. A copy of information from such website has been provided for the readers' convenience and is attached hereto as Exhibit A.

B. Note further that the term "angiogenic cascade" is set forth in the first paragraph of this article. Another use of the questioned terminology may be found on website of the University of Pittsburgh, Department of Molecular Genetics and Biochemistry, regarding Nathan Bahary, M.D., Ph.D., at http://www.mgb.pitt.edu/personnnel/Bahary_Nathan.htm. As may be seen, the term "genetic cascade" is used in connection with vasculogenesis in the first paragraph of the second page. A copy of information from such website is attached hereto as Exhibit C.

As succinctly pointed out above, Appellant has used "multifactorial and non-specific" to describe or characterize the potentialities of stem, germinal, and pluripotent cells. Appellant believes that the Patent and Trademark Office (hereinafter "PTO") should take Official Notice of the fact the term "pluripotent" is well known to those in the medical art to describe versatile (multifactorial) cells that are uniquely capable of effecting more than one organ or tissue, i.e., non-specific. "Differentiation" is understood by those skilled in the medical art to relate to the sum of the developmental processes whereby apparently unspecialized cells, tissues, and structures attain their adult form and function. "Morphogenesis" is understood by those skilled in the medical art to define the formation and differentiation of tissues and organs. Those skilled in the medical art would understand from Appellant's disclosure that multifactorial and non-specific cells can be a germinal cell (page 48, lines 6-8) or a stem cell (page 48, lines 13-15). However, not all stem cells are multifactorial and non-specific. Multifactorial and non-specific stem cells have the "versatility and non-specifically" to effect the formation of both an organ (such as a new artery) and cardiac tissue (composed of new cardiac myocytes).

As pointed out above, an applicant is not required to define well-known medical terminology that would be readily understood by one skilled in the art. Additional confirmation of such understanding by one skilled in the art may be found in the Second Supplemental

Declarations of Drs. Richard Heuser and Andrew C. Lorincz, at paragraphs 6 and 10 of such Declarations, which state that cellular growth factors are understood to include multifactorial and non-specific cells. It was error for the Examiner to fail to address the evidentiary value of these Declarations because they relate to the meaning of the questioned language.

In summary, one skilled in the medical art would understand that Appellant's above description of multifactorial and non-specific cells as including stem cells is consistent with the knowledge of the art and would have no difficulty in understanding the scope of protection sought by the claims. Accordingly, the Examiner's rejection of the language contained in claim 245 under 35 U.S.C. §112, second paragraph, for indefiniteness must fail for lack of a sound factual basis.

Rejection of Claims 248, 249 and 252 Under 35 U.S.C. §112, first paragraph

Claims 248, 249, and 252 stand finally rejected under 35 U.S.C. §112, first paragraph, "as failing to comply with the written description requirement." The Examiner, on page 4 of the Final Rejection, referred to page 4 of the previous Office Action of November 28, 2003, to provide a basis for the rejection of these claims. The Examiner considered that the terms "intravenous injection of cells," "intraluminal injection of cells," and "angioplasty delivery of cells" did not describe the subject matter of the invention in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Appellant respectfully believes that a reasonable reading of the specification by one skilled in the medical art leads to an opposite conclusion and provides the following explanation.

Initially, Appellant points out that compliance or lack thereof with the "written description" requirement of the statute is a question of fact and must be decided on a case-by-case basis. The initial burden rests with the Examiner to proffer evidence and/or sound reasoning why those skilled in the art, upon reading an applicant's disclosure, would not understand that the applicant was in possession of the claimed invention. See MPEP Section 2163.04 and the authorities cited therein.

The written description requirement does not require an applicant "to describe exactly the subject matter claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize what he invented and what is claimed." See In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ 2d 1614, 1618 (Fed. Cir. 1989). All that is required is that as of the filing date, the invention be conveyed with reasonable clarity to those skilled in the art that he was in possession of the claimed subject matter. See Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 1945 USPQ 2d 1111, 1117 (Fed. Cir. 1991). Appellant's specification, at page 45, line 1 to page 46, line 16 contains a statement of Appellant's invention commensurate in scope with the claims here on appeal. Numerous administration species for delivering therapeutic agents to patients, including intravenous, intraluminal, and angioplasty, and numerous growth factors suitable for use in the invention are described. Accordingly, the mere absence of actual working examples in the specification standing alone does not support the Examiner's conclusion that the statutory requirements are violated.

The Examiner has apparently cited Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ 2d 1961, 1966 (Fed. Cir. 1997) for the proposition that "the description requirement" requires a showing of reduction to practice to establish possession of the claimed invention. Lockwood does not change the standard for showing possession of the claimed

invention set forth in In re Gosteli. Rather, Lockwood sets forth a "variety of ways" that possession can be established, one of which is by showing reduction to practice. In this regard, the disclosure, at page 45, line 1 to page 46, line 16, includes the claimed administration techniques, as well as a variety of growth factors that lead to the claimed result, i.e., the growth of new cardiac muscle and new arteries.

The gravamen of the Examiner's position is that Appellant's description on page 45 of the specification of intravenous, intraluminal and angioplasty delivery modes "is limited to use of proteins or nucleic acids (genes or [other, sic] genetic material)" and that there is no suggestion in the specification, "that cells should be administered intravenously or intraluminally." The Examiner states that, "The specification defines 'growth factors' as comprising cells but does not define 'genetic material' as comprising cells." This statement is erroneous because it is clear from the specification that growth factors are included in the genus "genetic material." In this regard, see page 46, lines 6 and 7 of the specification where it is described that cells and growth factors are types of genetic material. Page 45, in fact, states, at lines 28-29, that "an appropriate gene or other genetic material" may be inserted (emphasis added). The prophetic example, in words, at lines 6 and 7 on page 46 describes that cells, genes, and/or growth factors (or other genetic material) are "placed" adjacent to dead cardiac muscle to grow new muscle and new arteries. Such passage clearly discloses that cells are included under the genus "genetic material." These descriptive words are equivalent to the language recited in the claims. The passages cited by the Examiner as indicating that cells are not genetic material do not, in fact, support such contention. Rather, such passages are consistent with Appellant's use of the term "genetic material" because such passages merely confirm that genes, like cells, are members of the genus "genetic material." The Examiner's conclusion that, "Clearly, this

section of the specification is limited to the use of proteins and nucleic acid (genes or genetic material)" is inconsistent with the disclosure at page 45, lines 13-16 because "other genetic material" is contemplated, and genetic material includes cells. Thus, the Examiner's contention is erroneous because it overlooks the fact that genes and cells are described as members of the same genus and that the cited passages are consistent with such description.

Viewed in another way, the Board's attention is also directed to page 44, lines 19-29 and page 45, lines 19-23 of the specification where it is stated that growth factors (the Examiner, at page 5, lines 13 and 14 of the Final Rejection, admitted that growth factors include cells) may be inserted with any of the implant techniques of the invention. The Examiner's admission should serve to conclusively resolve this issue because growth factors include cells, as well as other types of growth factors.

In addition, Appellant's specification, at page 46, lines 3-7 describes seeding with cells and other genetic material to grow new muscle and new arteries. Seeding, of course, is a broad term that is understood by those skilled in the medical art to cover intravenous, intraluminal, angioplasty, as well as other delivery modes. Thus, there is no question that Appellant broadly disclosed the administration of cells by intravenous, intraluminal, and angioplasty delivery techniques, as well as by other techniques.

As evident from the above discussion, all of the limitations of the claims at issue appear in the specification. Statements in the specification constitute evidence that must be weighed in establishing a *prima facie* case. See In re Margolis, 785 F.2d 1029, 1031, 228 USPQ 940, 942 (CCPA 1986). The Examiner has the burden of initially establishing a *prima facie* case of unpatentability. See In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ 2d 1443, 1445 (Fed. Cir. 1992). Appellant notes that the Examiner has failed to establish a factual basis sufficient to

support a *prima facie* case of "lack of description." Appellant submits that the Examiner has not articulated why the specific disclosure in the specification referred to by Appellant above fails to provide descriptive support for the claimed subject matter. Accordingly, Appellant believes that the Examiner's rejection under 35 U.S.C. §112, first paragraph, for failure to satisfy the written description requirement must fail for lack of a sound factual basis.

From the foregoing discussion, the Examiner's statement that the specification "does not define 'genetic material' as comprising cells" is patently incorrect, and thus it cannot reasonably be concluded that the specification does not convey with reasonable clarity to those skilled in the art that Appellant was in possession of the invention of the subject matter of claims 248, 249, and 252 as of the filing date of the subject application.

Furthermore, Appellant submitted objective evidence in the Second Supplemental Declarations of Drs. Heuser and Lorincz in rebuttal of the Examiner's rejection. These Declarations were submitted with Appellant's Letter dated July 26, 2004, entry of which was noted by the Examiner on page 2 of the Final Rejection. The Board is referred to paragraph 10 of each Declaration where it is concluded that, "such skilled person would further understand that the disclosures on pages 45 and 46 describe genetic material to include appropriate genes and cells." The Examiner must weigh Appellant's objective evidence proffered in paragraphs 6 and 10 of the Second Supplemental Declarations of Drs. Heuser and Lorincz in meeting the burden of establishing a *prima facie* case of inadequate description. cf. In re Alton, 76 F.3d 1168, 37 USPQ 2d 1578 (Fed. Cir. 1996). Said paragraphs 6 and 10 of these Declarations raise genuine issue of material fact regarding what the specification disclosed to one skilled in the art. The Second Supplemental Declarations of Drs. Heuser and Lorincz confirm that one skilled in the art would understand that Appellant's specification described genetic material to include

cells; and, therefore, the burden of going forward with evidence to the contrary shifted to the Examiner to show that one skilled in the art would not so understand the specification.

In the Final Rejection regarding the written description requirement, the Examiner apparently ignored the conclusions reached by Drs. Heuser and Lorincz in their above-mentioned Second Supplemental Declarations; namely, that cells are included in the description of the invention. The Examiner should have considered paragraphs 6 and 10 in said Second Supplemental Declarations because such Declarations contain evidence that these two skilled physicians understand that cells are described by the term "genetic material" and further that cells are understood to be described as materials which may be delivered in accordance with the modes mentioned at page 45, lines 13-16 of the specification. It is incumbent upon the Examiner to articulate how the Declarations failed to overcome her initial case for rejecting the claims in issue. In re Oetiker, supra. Therefore, the Examiner failed to weigh all the evidence in the record and, perforce, erred as a matter of law. cf. In re Alton, supra.

To place the written description rejection in proper perspective, it is noted that the appealed claims are those elected following a species restriction requirement between genes and cells. Although Appellant elected to prosecute the claims directed to cells, the specification is not so restricted. It is clear that Appellant has disclosed, for example, the genus genetic material, the subgenus cells, and the species stem cells, and thus fully provides descriptive support for the invention in the instant application. It is also clear that the specification includes genes as a subgenus under the genus genetic material. The specification was written to utilize generic terms and expressions to convey information regarding all subgenuses and species. Appellant believes that the Examiner failed to take such perspective into account when making this rejection and thus erroneously required that a strict antecedent basis for all species and administration

techniques be set forth in an exemplary manner whenever a generic term is used in the specification. At pages 5 and 6 of the Final Rejection, the Examiner pointed to various passages in the specification that purported to show that portions of the specification were limited to genes or genetic material. Such conclusion is erroneous for at least two reasons. First, as demonstrated above, the term genetic material includes cells. Second, a gene is a subgenus of genetic material. Therefore, such passages merely confirm to one skilled in the art that Appellant contemplates such materials. The cited passages are consistent with Appellant's use of broad terminology and merely discuss or exemplify one subgenus or specie that may be used in accordance with such passage. Certainly, such passages are not inconsistent with the terminology. Appellant's disclosure, coupled with the evidence proffered by the Declarations of Drs. Heuser and Lorincz far outweighs the case for rejecting claims 248, 249, and 252 for lack of description articulated by the Examiner.

Appellant observes that the rejection appears to be based upon a hypertechnical application of 35 U.S.C. §112, first paragraph, which should be reversed in view of the interpretation given this statutory requirement in a line of decisions exemplified by In re Robins, 429 F.2d 452, 166 USPQ 552 (CCPA, 1970); In re Borkowsky, 422 F.2d 904, 164 USPQ 642 (CCPA, 1970); and In re Wakefield, 422 F.2d 897, 164 USPQ 636 (CCPA, 1970).

Rejection of Claims 248 and 249 Under 35 U.S.C. §112, first paragraph

Claims 248 and 249 stand finally rejected under 35 U.S.C. §112, first paragraph, "as failing to comply with the enablement requirement." The Examiner further stated in the Office Action of November 30, 2003 that, "The claim(s) contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with

which it is most nearly connected, to make and/or use the invention." Although the Examiner's above-mentioned statement of the rejection failed to set forth any specific or cogent grounds for the rejection, Appellant's understanding is that the rejection is based on a lack of enablement for the administration of cells by intravenous and intraluminal techniques to a patient's heart to achieve repair. Appellant respectfully disagrees that the invention defined in the claims fails to comply with the enablement requirement of the statute.

It is apparent, based upon the Examiner's remarks in the Final Rejection, the Examiner considered that claims 248 and 249 are directed to a method for the repair of dead/damaged portions of a human heart. However, such remarks are erroneous because these claims require only growth of new cardiac muscle and a new artery. In view of such erroneous reading of the subject matter of the claims, the rejection of claims 248 and 249 should be reversed by the Board for failure to address the claimed subject matter. For the sake of completeness, Appellant has addressed all issues raised by the Examiner, whether or not they are directed to the claimed subject matter.

Initially, Appellant wishes to address an important issue underlying the instant appeal, i.e. consistency of examination standards applied by the PTO. The PTO is obligated to apply uniform standards of examination to maintain prosecution integrity and thereby ensure that administrative due process is accorded to all applicants.

Appellant believes the Examiner has applied inconsistent standards in her concurrent examinations of the instant application and *vis-à-vis* recently granted U.S. Patent No. 6,844,312, issued on January 18, 2005 to Weiss et al. and attached hereto as Exhibit D (hereinafter "Weiss patent"). This patent generally relates to and contains broad claims to the use of stem cells to

treat Parkinson's and other diseases. This issue could not have been addressed earlier because the Weiss patent did not issue until after the date of the Final Rejection.

The Weiss patent, like the present invention, broadly claims treating a patient with stem cells to achieve a new result, i.e., Weiss ameliorates Parkinson's disease by growing "new" neurons, and Appellant grows new cardiac muscle and a new artery. The file history of the Weiss patent reveals that the Examiner, unlike in the prosecution of the instant application, never challenged the enablement of the disclosed invention regarding the preparation or handling of stem cells, the enablement of intravenous and intraluminal stem cell administration techniques, and stem cell dosages or cell concentrations. The Examiner's sole challenge was to the scope of Weiss' novel therapeutic mixture. In contradistinction, in the prosecution of the present invention, the Examiner concluded that enablement was not present based in part upon the above enumerated stem cell factors. The inconsistency between the respective prosecutions is especially egregious in view of the fact that the present invention claims the use of old materials and old techniques – not the use of new compositions. Moreover, unlike in the Weiss prosecution, Appellant has proffered objective declaration evidence, which raises genuine issues of material fact regarding what the instant application disclosed to enable one skilled in the medical art to make and use the claimed invention, thereby further highlighting the inconsistency between the respective prosecutions.

It is important to note that the first paragraph of the statue requires nothing more than objective enablement, and it is of no importance whether such teaching is set forth by use of illustrative examples or by broad terminology. As a general matter, an application disclosure which contains a teaching of how to make and use the invention in terms which correspond in scope to those used in describing the invention sought to be patented is considered to be in

compliance with the enabling requirement of the statue. In re Marzocchi, 58 CCPA 1069, 439 F.2d 220, 169 USPQ 367, 369-370 (1971). Further, "Section 112 does not require that a specification convince persons skilled in the art that the assertions therein are correct." [Emphasis added]. In re Robins, supra.

The questioned intravenous and intraluminal administration techniques were well established in the medical art prior to Appellant's invention. That cells, including stem cells, were well known and characterized prior to Appellant's claimed invention is also an established fact. Another established fact that stem cell banks were created as early as the 1950's indicates that those skilled in the medical art were familiar with harvesting, handling, culturing, preserving, separating, and storing, etc. such stem cells. Dr. Elia's contribution to the medical art as it pertains to the claims on appeal, however, was that new cardiac muscle and a new artery could be grown through use of a new combination of old administration techniques and old cellular materials. Knowledge of the above facts compels the conclusion that one skilled in the medical art could read Appellant's disclosure of the invention and the claims in issue and reasonably determine that such disclosure would enable one skilled in the art to make and use the claimed invention without recourse to more than routine experimentation. Certainly, the expert opinions of Drs. Heuser and Lorincz confirm this conclusion.

The evidence relied upon by the Examiner in reaching the conclusion of lack of enablement consists of the Strauer et al. (hereinafter "Strauer") publication cited by Appellant as Exhibit I in the Amendment filed February 17, 2004, and the Deb et al. (hereinafter "Deb") publication cited by Appellant as Exhibit II in the Amendment filed February 17, 2004. Both publications bear a date later than Appellant's filing date.

The Examiner relied on Strauer as evidence of non-enablement of the claims reciting intraveneous administration of cells. At the bottom of page 7 of the Final Rejection, the Examiner concluded that Strauer is "not particularly relevant" to the rejected claims because such claims are directed to intravenous and intraluminal administration techniques. Appellant points out that Strauer's technique and intraveneous administration are both types of intraluminal administration.

Strauer was described by the Examiner at page 12 of the Final Rejection to utilize "a specialized form of intraluminal delivery, specifically, balloon catheter injection" where high-pressure injection was utilized while the angioplasty balloon was inflated to avoid a "wash-away" effect of standard intraluminal injection. The word "specialized" appears to be that of the Examiner, as it is not used by Strauer to characterize his process. In any event, whether or not the technique of Strauer may be characterized as "specialized," it is evident that many other techniques may be used to perform the claimed method; thus, disclosing the specific technique of Strauer is not required to constitute enablement of Appellant's invention. In this regard, Wollert et al. (hereinafter "Wollert") cited as Reference AP in Appellant's Third Information Disclosure Statement, mailed July 27, 2004, utilized a procedure essentially the same as that disclosed by Strauer, except that Wollert utilized a conventional, off-the-shelf angioplasty balloon to infuse cells without describing any need for high pressure. Appellant cited Wollert as evidence that high-pressure injection of cells, such as reported by Strauer, is not required to achieve heart repair and that providing a sufficient number of cells and preventing remigration are not insurmountable problems, as alleged by the Examiner. It was error for the Examiner not to consider the evidence contained in Wollert. The Wollert publication verifies this fact, and the Examiner has provided no rebuttal thereof. Accordingly, Appellant's failure to mention high

pressure in the specification is of no moment because Wollert demonstrates that successful implantation does not require high-pressure infusion.

Strauer did not state that other administration techniques, such as intramuscular or intravenous, were inoperative but instead considered such techniques not as effective and concluded that "intracoronary administration obviously seems to be advantageous..." (Page 1917, left column, lines 26 and 27). A fair reading of the text at page 1917, first and second full paragraphs of the left column, indicates that Strauer did not consider intravenous administration to be inoperative, as erroneously alleged by the Examiner, but was simply not preferred on the basis that multiple administrations could be required. There is no evidence that Strauer, in fact, conducted any side-by-side experimentation with any other delivery modes to support such consideration, and thus such passage is speculative. The Examiner failed to appreciate that to have an enabling disclosure, an applicant is not required to foresee, invent, and disclose future improvements to standard, known techniques. Under current law, an applicant is not required to foresee, invent, and disclose improvements and enhancements to the basic invention to provide an enabling disclosure. Merely because Strauer reported that his high-pressure push technique provides good results does not mean that Appellant's specification does not provide an enabling disclosure as of the filing date of the subject application. cf. Hormone Research Foundation v. Genetech, Inc., 904 F.2d 1558, 15 USPQ 2d 1039 (Fed.Cir.1990). All an applicant is required to do is provide a disclosure that one skilled in the art can understand and then follow to make and use the invention. Thus, any failure to disclose a later developed technique has no bearing upon enablement. The Examiner also relies upon a passage of Strauer where "shortcomings" of intravenous and intramuscular administrations are discussed. Again, Strauer does not indicate that intravenous and/or intramuscular administrations are not operative but only that such

techniques are less efficient than their high-pressure intraluminal technique. See the first and second paragraphs, left column, on page 1917 of Strauer. By stating that his technique "seems to be advantageous...and may also be superior," to other forms of injection, Strauer does not raise a genuine issue of material fact and clearly does not establish inoperability of other forms of administration, as alleged by the Examiner.

The Examiner's above analysis overlooks the commonly known fact that both intravenous and intraluminal administration are well established in the medical art as techniques for introducing various substances into the body of a patient. Intravenous administration, in particular, is routinely used for such introduction. Inserting a substance into a vein of a patient, where it mixes with blood and is transported throughout the body by the circulatory system, results in treatment of a desired area. Inasmuch as all blood circulates through the heart, the heart itself is a prime candidate to be treated by intravenous administration. It is also well established in the medical art that multiple dosages are utilized, via intravenous and intraluminal administration, until a desired medical result is achieved.

It is also pointed out that in the prosecution of the Weiss patent, the Examiner, unlike in the instant application, made no enablement challenge to the broadly disclosed and claimed administration techniques, including intravascular and intramuscular, even though the treated site was the brain – a site more remote than the heart. See column 8, lines 25-37 of the Weiss patent in this regard.

In the challenge to the qualifications of Drs. Heuser and Lorincz at page 7 of the Final Rejection, the Examiner raised generalized concerns regarding the properties and handling of cells. Such concern by the Examiner amounts to an expression of opinion rather than factual evidence. The properties of cellular materials were well established and well known in the

medical art prior to Appellant's filing date. Official Notice can be taken that stem cell isolation and culture techniques have been known and used decades prior to Appellant's filing date. In this regard, Appellant submits four publications (attached hereto as Exhibits E, F, G, and H) which confirm the above-mentioned facts and which are believed to fully resolve any issue created by the Examiner's concerns. While Exhibits E-H speak for themselves, Appellant makes the following comments regarding such Exhibits. Exhibit E is an article published in 200-2 by Pediatric Transplantation entitled, "Milestones in the Development of Pediatric Hematopoietic Stem Cell Transplantation – 50 Years of Progress." This publication is a review article summarizing fifty years of practice, and thus supports the fact that stem cell handling and preparation techniques have been known for decades. Exhibits F, G, and H further demonstrate that stem cell isolation and culture techniques have been known and used decades prior to Appellant's filing date and constitute probative evidence that fully rebuts the Examiner's unsupported "concerns."

The Examiner's challenge to the qualifications of Drs. Heuser and Lorincz also opined that stem cells are not like other drugs routinely administered in the art. Appellant respectfully disagrees with such unsupported opinion because bone marrow stem cell harvesting and administration are well-established protocols. The Examiner also opined that, "they [cells] have to be handled delicately so as to avoid mechanical or chemical rupture of the cell membranes." This opinion is negated by the factual evidence that Strauer utilized "high-pressure injection," which functioned for the intended purpose and apparently did not result in mechanical or chemical rupture. There is no evidence to support the Examiner's opinion, and the evidence contained in Strauer rebuts such opinion.

From the above discussion, it is evident that the Examiner has raised unfounded "concerns" regarding cell handling and preparation and has failed to provide any evidence supporting the validity of such concerns. These concerns are based upon the Examiner's unsupported opinion and speculation and are not entitled to evidentiary weight. On the other hand, Appellant has provided objective evidence rebutting the Examiner's unsupported opinion, which indicates that the Examiner's concerns are speculative and have already been addressed and resolved in the medical art for years prior to Appellant's filing date. Thus, the Examiner's concerns are unfounded and are not supported by any evidence of record, whether used to challenge the qualifications of Drs. Heuser and Lorincz or to challenge the enablement of claims 248, 249, and 252.

At pages 14 and 15 of the Final Rejection, regarding the enablement of claims 248 and 249, the Examiner admits that Deb "provides evidence that bone marrow cells, administered intravenously, can migrate to the heart." Such admission should end any speculation as to the operability of intravenous administration of cells as disclosed in Appellant's specification. Inasmuch as intravenous administration is a specie of intraluminal administration, Appellant believes that the Examiner's admission pertains to both types of administration.

The Examiner also alleged that Appellant cited Deb for the proposition that, "human bone marrow can be used as a source of extracardiac progenitor cells capable of de novo cardiomyocyte formation." Such allegation is erroneous because it was Deb, (at page 2 in the Conclusions section) rather than Appellant, that made such statement. Instead, Appellant cited Deb to rebut the Examiner's erroneous contention that intravenously injected cells would not migrate to the heart. Clearly, Deb verified such migration.

Moreover, the Examiner stated at page 15 of the Final Rejection, "The Deb et al. publication is the only evidence that addresses administration of cells at a site other than exactly at the infarct zone." Such statement is clearly erroneous. Strauer administers an intracoronary (intraluminal) injection near the infarcted zone. On page 1914 in Figure 1, Strauer clearly states the "catheter enters the infarct-related artery and is placed above the border zone of the infarction." The cells must migrate in order to physically get outside of the infarct-related vasculature and into the dead heart muscle. As a result of said migration, "The cells are therefore able to reach both the border and the infarcted zone" of the heart. Wollert produced similar results to those of Strauer, with the exception that Wollert delivered autologous bone marrow cells (BMC's) via the central lumen of an off-the-shelf balloon catheter without the need for pressure infusion. The work reported by Ziegelhoeffer et al. (hereinafter "Ziegelhoeffer"), cited for the first time by the Examiner on page 25 of the Final Rejection, provides further evidence of the successful intraveneous administration of cells at a site other than the infarcted zone. Thus, Strauer, Deb, Wollert, and Ziegelhoeffer all provide evidence that migration to the heart occurs with intravenous and intraluminal administrations of cells.

The Examiner has criticized Deb for not providing sufficient dosages to effect heart repair. Such criticism is misplaced because claims 248 and 249 do not require heart repair, and Deb did not attempt heart repair as implied by the Examiner. Deb reported human autopsy evidence of cardiomyocyte formation, which validates the claimed invention. All of the patients in the Deb study received routine bone marrow transplantation dosages, which had been well-established protocol for decades. Certainly, the amount of cells administered by Deb was sufficient to grow new cardiac muscle. In any event, Deb, in the table on page 1248, makes it clear that the patients all had some form of leukemia; and at lines 14 and 15 of the same page

states that, "no patients in our study group had histological evidence of myocardial inflammation." Thus, it is of no moment whether or not the amount of cells injected by Deb was sufficient to cause heart repair simply because, as stated by Deb, the study was not directed to heart repair. Strauer speaks of remigration and theorizes that intravenous application would possibly require many circulation passages to enable sufficient cells to come into contact with the heart. Further, Strauer merely states, at page 1917, first column, lines 42-46 that, "[p]resumably, ..., fewer cells were lost ... " due to remigration when delivering the cells by intracoronary administration. The Examiner has not identified any teaching in Strauer that intravenous administration techniques would be inoperative or that it would require more than routine experimentation to determine the number of passages of infused cells required to achieve the desired result. Multiple administrations of cellular material are common in the medical art, as evidenced by Strauer, who contemplated using up to seven infusions for his intracoronary technique. Thus, one skilled in the art utilizing an intravenous administration would understand that multiple dosages could be utilized for achieving new cardiac muscle growth, new artery growth, and heart repair, as illustrated by Strauer. It is a notoriously well-known and common practice in the medical art to administer multiple dosages of substances, such as cells, intravenously.

The Examiner's attempt, at pages 14 and 15 of the Final Rejection, to couple the teaching of Deb with the disparate teaching of Strauer to establish that the use of "intravenous administration of cells to repair a dead or damaged portion of a heart has not been achieved due to the obstacles involved with getting sufficient numbers of cells to the dead/damaged site and preventing them re-migrating away from the site" is inapt. Appellant points out again that claims 248 and 249 do not require heart repair, and thus the Examiner's statement is irrelevant to

the claimed subject matter. In any event, the Examiner has pointed to no evidentiary basis in this record to support such a conclusion.

As stated above, coupling Deb and Strauer is obviously inappropriate because Deb, unlike Strauer, is not attempting to repair a heart. A more reasonable reading and understanding of the respective teachings of Strauer and Deb leads to the conclusion that intravenous administration of cells would result in the growth of new cardiac muscle and new arteries. A fair reading of Strauer clearly indicates that intravenous administration would be operative and likely could involve multiple circulations. See Strauer at page 1917, second paragraph of left column, in this regard.. A fair reading of Deb indicates that intravenously administered stem cells travel to the heart and produce cardiomyocytes. Thus, it would be well within the skill of the art to select an appropriate number of cells (dosage) and number of infusions to achieve the desired result for reasons fully addressed later by Appellant at pages 60-63 of this Brief.

Providing a sufficient number of cells and preventing "remigration" are not shown by the Examiner, in fact, to be insurmountable problems because, as pointed out earlier, Wollert is operative to repair a human heart. Appellant again points out that claims 248 and 249 are not directed to heart repair. In any event, as a repair occurred, Wollert clearly must have provided a sufficient number of cells and overcome problems, if any, associated with "remigration." Rather, such alleged problems concern efficiency, not operability, and do not constitute "evidence of nonenablement" as alleged by the Examiner. As will be noted below, Drs. Heuser and Lorincz disagree with the Examiner's conclusion. Once again, the Examiner has fabricated problems that extend beyond the disclosure and claims rather than addressing such expert opinions. It is well established that an invention does not need to work in an optimum manner to meet the requirements of the patent statutes.

In summary, Appellant believes that the Examiner's evidence of lack of enablement, which comprises the Examiner's erroneous assessment of Strauer and Deb, as discussed above, when considered *vis-à-vis* the evidence of enablement provided by Appellant's specification combined with a fair and reasonable reading of Strauer and Deb, coupled with Wollert, fails to establish a *prima facie* case of lack of enablement under current law. Thus, this rejection should be reversed.

Assuming, *arguendo,* that a *prima facie* case was established by the Examiner, the record contains additional objective evidence in the form of declarations proffered by Appellant that is ample to rebut any such case. During an interview on May 22, 2003, the Examiner stated that an expert opinion from an interventional cardiologist would be helpful in regard to establishing the operability of the claimed methods. Based upon such statement, Appellant identified Dr. Richard Heuser. Appellant also identified Dr. Andrew Lorincz because he is highly skilled in genetics, a field of medicine also clearly related to the claimed invention. Appellant submitted initial Declarations of Drs. Heuser and Lorincz as evidence of what the application disclosed to one skilled in the art. Appellant subsequently proffered two Supplemental Declarations of Drs. Heuser and Lorincz. In addition, a Third Supplemental Declaration of Dr. Heuser (attached hereto as Exhibit I) is submitted to respond to the criticisms raised by the Examiner in the Final Rejection. This Brief presents the first opportunity for Appellant to respond to such criticisms.

In the Final Rejection, at page 7, the Examiner determined that the original and two Supplemental Declarations under 37 CFR 1.132 of Drs. Heuser and Lorincz were insufficient to overcome the initial enablement rejection. The Examiner challenged these Declarations, in the Final Rejection, on two grounds; namely, 1) "while it is clear that Drs. Heuser and Lorincz are accomplished physicians, it is noted that none of the Declarations...or the Supplemental

Declarations...report experience with cellular therapy as required by the instant claims." (page 7); and 2) "are based upon evidence that is found to be either irrelevant, not commensurate in scope with the claims, or relying upon methods which were not disclosed in the specification as originally filed." (page 10). Regarding the first ground, as will be demonstrated below, Drs. Heuser and Lorincz are eminently qualified to render their respective opinions. Regarding the second ground, these opinions are based upon Appellant's specification and are not, as erroneously alleged by the Examiner, based upon any other extraneous evidence.

On July 26, 2004, Appellant submitted Second Supplemental Declarations of Drs. Heuser and Lorincz, which contained additional information regarding their respective qualifications to render their expert opinions. Dr. Heuser provided additional background information affirming his knowledge of "cell therapy." Dr. Lorincz provided information indicating his familiarity with stem cell technology, including bone marrow preparation. The Examiner, at page 10 of the Final Rejection, further challenged their respective qualifications by raising new issues. Appellant, in an attempt to answer such newly raised issues, submitted a Third Supplemental Declaration of Dr. Heuser directed to the new issues raised by the Examiner. Paragraph 5 of the attached Third Supplemental Declaration provides clarification that the device described in Dr. Heuser's U.S. Patent No. 6,190,379 has been utilized to administer protein and/or muscle cells to the myocardium. Dr. Heuser also provides further detail regarding his role in Bioheart, Inc.'s trials involving the administration of cells to the heart. Appellant considers that such additional information fully responds to the Examiner's newly raised concerns and believes that all issues of qualification are satisfied, particularly because the Examiner has not cited any evidence that recognizes "cellular therapy" as a medical specialty and, as a consequence, any qualifications pertaining to "cellular therapy" are unknown and undefined.

It is apparent that the clinical investigation team conducting the Strauer experiments comprised cardiologists and other highly skilled medical professionals, and that the Examiner has not specifically pointed out where the Strauer team possessed expertise different from Drs. Heuser and Lorincz. Appellant further notes that the investigative team of the Murry publication was apparently led by Charles E. Murry, M.D., Ph.D., Dept. of Pathology, University of Washington. Clearly, the Strauer and Murry teams do not appear to exhibit an expertise in heart repair that significantly differs from that of Drs. Heuser and Lorincz.

Regarding the claimed intraluminal and intravenous administration techniques, Appellant notes that Dr. Heuser's CV indicates extensive experience in the administration of various materials to the heart. For example, Dr. Heuser's CV is replete with medical journal articles, book chapters, and books dealing with intraluminal placement of various appliances and devices, including those described by Strauer. Moreover, the Board is requested to take Official Notice that physicians, such as Drs. Heuser and Lorincz, are quite familiar with the well-known administration techniques of intravenous and intraluminal injection. Individuals having far less qualifications than physicians routinely perform cellular intravenous injections, such as blood/bone marrow transfusions.

Regarding cells and administration techniques, Dr. Heuser's Second Supplemental Declaration states that he was granted U.S. Patent No. 6,190,379 for a hot tip catheter. The Third Supplemental Declaration, at page 5, states that this catheter has been used for the delivery of protein and/or muscle cells to the myocardium. The Examiner indicated that the word "cell" does not appear in the patent. Appellant agrees with the Examiner that such word does not appear in the patent but points out that Dr. Heuser's Third Supplemental Declaration refers to the use of the device covered by the patent, not the disclosure of the patent.

The Examiner, at page 10 of the Final Rejection, alleged that there was no evidence to support Dr. Heuser's statement that he had worked in gene therapy. Such allegation is erroneous because it ignores the fact that a declarant's sworn statements constitute evidence, in and of themselves.

Dr. Heuser is a member of the Scientific Advisory Board of Bioheart, Inc., a world leader in cellular muscle repair of the myocardium. Dr. Heuser's Third Supplemental Declaration provides further detail as to his advisory role in the performance of trials involving cellular administration to the heart. Clearly, he is an expert in the field of medicine pertaining to the invention and would be recognized by his peers as eminently qualified to review the disclosure and claims and to render the expert opinions based thereon.

Appellant identified Dr. Lorincz as an expert because he is skilled in genetics – a field of medicine related to the claimed invention. Considering Dr. Lorincz's educational and professional experience, it is evident that he is also qualified to render an expert opinion regarding Appellant's enablement of the claimed invention.

Dr. Lorincz stated in his Second Supplemental Declaration that he is familiar with stem cell technology, including bone marrow preparation. Such familiarity, coupled with other work involving cellular products previously outlined in his CV, leads to the conclusion that a reasonable person being familiar with the medical art would recognize that Dr. Lorincz is highly qualified to render an expert opinion in the instant patent application. The Board's attention is directed to "Fluorescent Microscopy of DES-induced Morphologic Transformation in Unfixed, Cultured Cells" which appeared in Journal of Oral Pathology and Medicine and is located in the Bibliography section of Dr. Lorincz's CV. The Board's attention is also directed to "Biochemical Genetic Defects" published in the Journal of The Florida Medical Association and

located in the Editorials and Commentaries section of Dr. Lorincz's CV. Moreover, Dr. Lorincz personally informed Appellant's representative, Dr. Jerry W. Bains, of an unreported study involving Dr. Lorincz's assessment of stem cell infusions into patients to correct Hurler's Syndrome by transplanting cord blood stem cells. Dr. Lorincz's CV is replete with references to Hurler's Syndrome as well as other cellular studies. Dr. Lorincz is currently Chairman of Vitalflor, a company involved in the observation of cells in the microscopy assessment of vitally stained living cells and living organisms. Dr. Lorincz was granted the following three U.S. patents: No. 5,812,312 (incorrectly identified as Patent No. 5,812,314 heretofore in the record) entitled Microscope Slide; No. 6,239,906B1 entitled Flexible Microscope Slide; and No. 6,567,214B2 entitled Microscope Slide Having Culture Media and Method for Use. These patents relate to special stains useful in such assessments.

Appellant believes that the fact that the Declarants have diverse backgrounds and that each rendered an opinion stating that the specification enables one skilled in the art to make and use the claimed invention constitutes compelling, probative evidence. Appellant's belief is reinforced by the fact that Strauer's investigational team members had expertise in diverse fields. Accordingly, the above-mentioned qualifications of Dr. Heuser and Dr. Lorincz, in combination with the Examiner's admissions in the Final Rejection at page 10, lines 19 and 20 that, "Again, it is clear that Dr. Heuser is an eminent, highly accomplished cardiologist," and at page 11, lines 20 and 21 that, "Again, it is clear that Dr. Lorincz in an eminent, highly accomplished doctor," compel a conclusion that both doctors are qualified to present the expert opinions contained in their respective Declarations. Accordingly, the Examiner must weigh the objective evidence provided by these two medical experts, not summarily dismiss such evidence as somehow being submitted by non-qualified individuals. Such dismissal is error.

In the Final Rejection at page 7, the Examiner additionally took issue with the Declarations of Drs. Heuser and Lorincz by erroneously stating that Drs. Heuser and Lorincz relied on a number of publications to support their respective enablement opinions. Such publications were Strauer, Pagani et al., Hamano et al., Tse et al., and Perin et al. In fact, the Declarants placed no such reliance upon these publications; and thus, there is no nexus between the Examiner's criticism and the respective Declarations. The Board's attention is directed to Paragraph 9 of the Declarations, Paragraph 8 of the Supplemental Declarations, and Paragraph 9 of the Second Supplemental Declarations, where it is indicated that the Declarants relied only upon Appellant's indicated disclosure and claims to reach the conclusion that one skilled in the medical art, armed with the relied upon information, would be able to practice the method set forth in the claims without need for resorting to undue experimentation. The publications mentioned by the Examiner form no part of the information relied upon by the Declarants. Thus, the Examiner's reading of the respective Declarations was erroneous.

The Examiner stated, at page 10 of the Final Rejection, "Therefore, the opinions of Drs. Heuser and Lorincz are not found to be persuasive, as it is based upon evidence that is found to be either irrelevant, not commensurate in scope with the claims, or relying on methods which were not disclosed in the specification as originally filed." The preceding paragraph demonstrates that the Declarants relied only upon Appellant's specification and claims; and thus the Examiner erroneously read the above-mentioned Declarations. The Examiner's sole criticism relating to the scope of the claims is that such scope is broader than that of the administration technique of Strauer. Clearly, Strauer's technique falls within the claims and may constitute an improvement to the broader techniques disclosed in the specification. The scope of the claims is fully supported by the disclosure, and thus the Examiner's criticism has no merit.

Appellant submits that the Examiner's enablement determination is flawed because the Declarations of Drs. Heuser and Lorincz were not accorded due weight. These Declarations were proffered as objective evidence in rebuttal of the Examiner's initial determination that the claimed invention failed to comply with the written description and enablement requirements of the statute. Appellant believes that these experts' Declarations raise genuine issues of material fact regarding what the specification discloses to one skilled in the art. cf. In re Alton, supra.

It is well established that questions of whether a specification provides adequate written description and/or enablement of the claimed subject matter are issues of fact. The Declarations of Drs. Heuser and Lorincz raised genuine issues of material fact (evidence) regarding what the application disclosed to one skilled in the medical art, and the Examiner must weigh that evidence and render a decision based on the relative strength of Appellant's showing *vis-à-vis* her initial case for lack of enablement. The Examiner is charged with making sure that Appellant's objective evidence relied on guidance gleaned from the specification as filed and what was known to one skilled in the art and making sure that such evidence bears a reasonable correlation to the scope of the claimed invention.

The Examiner erred by dismissing the Declarations of Drs. Heuser and Lorincz without articulating a succinct explanation of how the Declarations failed to overcome her initial case for rejecting the claimed subject matter at issue. In re Oetiker, supra. The Examiner's dismissive conclusory statement that the Declarations were considered but not found to be persuasive does not rebut the thrust of Appellant's Declarations nor does it meet the spirit and letter of In re Oetiker, supra. It is well established that examiners, not being skilled persons in the art, must give weight to expert opinions rather than substitute their own opinion. See In re Neave, supra.

The standard for determining whether an applicant meets the enablement requirement of the statute was established in Mineral Separation v. Hyde, 242 US 261, 270 (1916). Although §112 of the statute does not use the words "undue experimentation," the Courts have interpreted enablement to require the person skilled in the art to make and use the invention without resorting to more than routine experimentation, In re Wands, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988). As recognized by the Court in Amgen, Inc. v. The Chugai Pharmaceutical Company, Ltd., 927 F.2d 1200, 18 USPQ 2d 1016 (Fed. Cir. 1991), the Wands factors are illustrative of, not mandatory to, finding a disclosure enabling. The present case illustrates the reason for that warning.

Although Appellant believes that the above arguments fully respond to the lack of enablement issue raised by the Examiner and should be dispositive of this issue, Appellant will hereinafter discuss the individual Wands factors for the sake of completeness.

It appears to Appellant that the basis for the Examiner's rejection for lack of enablement is stated on pages 19-20 of the Final Rejection wherein the Examiner concluded:

> Due to the large quantity of experimentation necessary to determine how to administer cells intravenously or intraluminally to achieve repair of a distant dead or damaged heart portion, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the contradictory state of the prior art, the unpredictability of targeting cells to a distant site, and the breadth of the claims, it is determined that undue experimentation would have been required of the skilled artisan to practice the claimed methods.

It is again pointed out that claims 248 and 249 do not require heart repair, and accordingly, the Examiner's conclusion is erroneously based upon an unclaimed feature of the invention. In any event, for completeness, Appellant will treat the Wands factors below.

Except for determining and evaluating the impact of the level of skill of those in the art regarding enablement, the above basis embodies the Wands factors. Obviously, the skill level in the art is important and necessarily impacts any analysis of the other Wands factors. In the Final Rejection regarding claims 248 and 249, the Examiner failed to specifically discuss or weigh the Wands factor relating to skill in the art, either alone or in combination with other related factors. Appellant believes that the Examiner's failure to discuss, evaluate, and weigh the impact of the skill level upon each of the other enumerated Wands factors leads to an erroneous analysis. One must first identify the skill level in order to adequately evaluate the other inextricably intertwined Wands factors. Once the skill level is considered along with other evidence, Appellant believes that a conclusion of enablement is compelled.

As mentioned in MPEP Section 2164.01(a), the Examiner must weigh all evidence related to the Wands factors (emphasis added). The decision in In re Wands led to the grant of a patent, as the Court found that the PTO's determination of unpredictability was not supported by the evidence in the record. In reversing the PTO, the court specifically noted that the evidence in the record supported a finding of predictability. The Court further noted that the skill level in the art was high and that known materials were utilized in the practice of the invention in weighing the evidence. The instant fact situation is similar to that of In re Wands because the skill level is also high and known administration techniques and known materials are also utilized in the practice of the invention. Appellant's evidence, in the form proffered by his experts, far outweighs any evidence regarding enablement supplied by the Examiner.

The Examiner's analysis of the Wands factor relating to the quantity of experimentation and amount of guidance required relies upon Strauer and Deb as evidence that large amounts of experimentation would be required to practice the claimed invention. As recognized by the

Court, such factors are illustrative of, not mandatory to, finding a disclosure enabling. See Amgen, supra. Appellant has already rebutted the Examiner's analysis of Strauer and Deb above, on pages 30 and 31 of this Brief, and such remarks need not be repeated. The Examiner's conclusion is at odds with the expert opinions of Drs. Heuser and Lorincz, which evince that one skilled in the medical art, armed with the knowledge of the disclosure, would be able to practice the method covered by the claims in issue without need for resorting to undue experimentation. The Examiner is merely basing such conclusion on unsound reasoning and mere opinion rather than upon material fact. Finally, considering that the skill level in the art is quite high, the amount of experimentation required to make and use the claimed invention would be *diminimus*.

Appellant believes that the Examiner has further mischaracterized Strauer, at page 16 of the Final Rejection, as evidence that, "a great quantity of experimentation would be required of the skilled artisan to practice the claimed method to achieve the required result." In fact, no experimentation was involved in Strauer's feasibility trials; instead, Strauer achieved the expected result in the absence of experimentation. A careful reading of Strauer reveals that work performed during a Phase I trial was used as a basis for the article. As further stated in the article, Phase I trials do not involve a randomly allocated blind control group. Such Phase I work did not involve experimentation but was merely a feasibility trial utilizing autologous cells from the patients' bone marrow aspirate as a whole, rather than as a subpopulation.

A reasonable reading of Strauer indicates that the authors relied upon the prior work of others in determining cell population and cell transplantation factors; and thus, Strauer performed little, if any, experimentation in these areas. It is clear that the work performed by Strauer involved the selection of known materials and administration techniques rather than conducting experiments designed to determine the effect of such materials and techniques.

Hence, the Examiner's reliance upon Strauer as evidence that undue experimentation would be required is erroneous.

At page 16 of the Final Rejection, the Examiner stated the following:

> The evidence as a whole indicates that intravenous administration of cells to repair a dead or damaged portion of a heart has not yet been achieved due to the obstacles involved with getting sufficient numbers of cells to the dead/damaged site and preventing them from re-migrating away from the site. As this problem has not yet been solved in the literature, and no suggestions for solving the problem are suggested in the specification as originally filed, a great quantity of experimentation would be required of the skilled artisan to practice the claimed method to achieve the required result.

Such statement does not take into account that claims 248 and 249 do not require heart repair and, thus, is irrelevant to such claims. In any event, the Examiner's assertion is erroneous and is rebutted by Strauer, Wollert, and Deb, as discussed throughout this Brief.

Accordingly, Appellant believes that the facts set forth above regarding Strauer do not support the Examiner's characterization of this evidence. Appellant believes that Strauer supports evidence of enablement of the claimed invention, not lack thereof. Like Appellant, Strauer used known administration techniques and known materials to achieve the new result of artery formation and heart repair. As demonstrated before in this Brief, Deb did not attempt heart repair, and performed <u>no</u> experiments directed toward the claimed results. Accordingly, Deb has probative value only regarding enablement for confirming that migration to the heart occurs upon intravenous administration of cells and that new cardiac muscle is grown. Based on Strauer and Deb, Appellant believes that the Examiner has failed to establish that large amounts of experimentation would be required to practice the claimed invention.

In regard to the amount of direction/guidance presented in the specification, Drs. Heuser and Lorincz have reviewed the specification and provided expert opinions based thereon that the invention defined in the claims is enabled by the specification. This is evidence that the specification provided sufficient direction and guidance to practice the invention of the claims in issue. The Examiner has failed to articulate wherein such disclosure relied upon by Declarants does not meet the necessary requirements for direction and guidance, and has not proffered any evidence to the contrary. Hence, the Examiner's comments amount to opinion, not evidence, and should be accorded no weight.

The next Wands factor addressed by the Examiner is the presence or absence of working examples. The Examiner generally concluded that the absence of working examples in the specification must be taken into account. Appellant does not disagree with such conclusion but believes that the presence of prophetic examples in the subject specification is entitled to probative weight when evaluating the totality of evidence. In this regard, the Examiner has failed to address the disclosure at page 46, lines 3-16. Such disclosure contains a prophetic example disclosing heart repair by seeding with cells immediately adjacent the dead cardiac muscle and growing new muscle and new arteries. Official Notice should be taken that "seeding" is a broad term, which includes intravenous or intraluminal injection, as well as other types of injection. One skilled in the art, reading page 46 in conjunction with page 45, would understand that "seeding" includes the intravenous and intraluminal modes found on page 45. Note further that Drs. Heuser and Lorincz based their opinions, in part, on such disclosure. Indeed, the MPEP Section 2164.02 specifically sanctions the use of prophetic examples as means for satisfying the enablement requirement of 35 U.S.C. §112, first paragraph. Of course, a prophetic example, unlike work actually conducted or results actually achieved, describes an

embodiment of the invention based on predicted results and serves to inform a person skilled in the art as to the working of the invention. It was error for the Examiner to deem that only working examples are relevant in the evaluation of this factor.

The next Wands factor addressed by the Examiner is the complexity of the invention. Appellant's disclosure is directed to skilled persons in the medical art, such as the Declarants. Obviously, subject matter that may appear complex and complicated to a non-skilled person is not complex and complicated to a person skilled in the medical art. It must be kept in mind that the present invention involves the administration of known materials using known administration techniques to achieve a new result, and complexity must be evaluated in view thereof. In other words, complexity may lie in the conception, but not in making and using the invention once the concept is understood.

The Examiner's reliance upon Murry to establish complexity is misplaced. Murry is not concerned with the subject matter of the claims at issue in this portion of the rejection; i.e., intravenous and intraluminal administration of cells to a human heart. Rather, Murry simply administers cells by intramuscular injection to a mouse. This administration technique is notoriously old and well known in the art – certainly not complex. Thus, the Examiner's erroneous reliance upon Murry to establish complexity is necessarily flawed because the respective administration modes and patients of Murry and those in Appellant's claims 248 and 249 are distinct.

It is noted that the Examiner further alleged that Strauer is illustrative of complexity, apparently relying upon the fact that Strauer utilized a high-pressure intraluminal injection technique to administer cells. This aspect of Strauer has been discussed extensively above and need not be repeated. In such prior discussion on pages 23-25 of this Brief, Appellant mentions

that Wollert successfully used an intraluminal infusion technique that did not require the use of Strauer's high-pressure technique. Such fact mitigates any inference of undue complexity in view of Strauer because Strauer's "specialized technique" is not essential to the practice of the invention.

In the discussion of the Wands factor involving complexity, the Examiner considered that more than one embodiment may be required in cases that involve chemical reactions and physiological activity, citing Ex parte Hitzeman, 9 USPQ 2d 1821 (BPAI 1987); In re Fisher 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); and Amgen Inc. v. Chugai Pharmaceutical co. Ltd., 927 F.2d 1200, 1212, 18 USPQ 2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991), and concluded that in the instant case no working embodiments were given. The Examiner's reliance upon such case law is inapt because these cases address current law regarding predictability determinations, not complexity. In fact, in the Amgen case, there was evidence of unpredictability in the form of testimony by expert witnesses. These cases are not controlling in the present situation where evidence of predictability is present in the respective Declarations. It is again emphasized that Drs. Heuser and Lorincz believe that the claimed results are predictable and that appropriate weight must be assigned to this evidence. In any event, Appellant's disclosure contains examples of various growth factors being utilized to form a new cardiac muscle and a new artery.

In view of the above remarks, Appellant submits that making and using the claimed invention is not complex as alleged by the Examiner but rather is a straightforward procedure utilizing known materials and administration techniques. The Declarants' enablement opinions confirm such submission.

The next Wands factor addressed by the Examiner is the state of the art. It is noted that the Examiner has cited no art involving the treatment of patients with either intravenous or intraluminal techniques. The Examiner, at page 18 of the Final Rejection, characterizes the art as, "the majority of publications form [sic] this time were geared toward intramuscular administration rather than intravenous or intraluminal administration techniques." Actually, the only publication prior to Appellant's April 21, 1998 filing date is that of Murry. Murry is directed only to intramuscular administration, and <u>no</u> prior art was cited regarding intravenous and intraluminal techniques. This analysis misses the point because the Examiner omitted the fact that intraluminal and intravenous techniques were well established in the art for other purposes prior to Appellant's filing date. What was not established was that these techniques could be utilized to administer cells to grow new cardiac muscle and new arteries.

The next Wands factor addressed by the Examiner is "unpredictability." The Final Rejection contains no objective evidence regarding this issue. The Examiner set forth no evidence and attempts to equate some unspecified "deficiencies of the evidence brought forth by Applicant" as evidence of unpredictability. Inasmuch as the Examiner failed to identify any such deficiencies, no probative weight can be accorded to support the Examiner's position. In contrast, Appellant has submitted strong, probative evidence in the Declarations of Drs. Heuser and Lorincz that the claimed invention is predictable.

The final Wands factor addressed by the Examiner is breadth of the claims. The Examiner observed, at page 18 of the Final Rejection, that, "although intravenous and intraluminal administration of certain drugs for certain effects may be routine, but intravenous and intraluminal administration of cells to repair dead or damaged heart tissue was not well-known in the art." Both aspects of this observation are correct. The Examiner has apparently

failed to comprehend that Appellant has used old and routine administration techniques and old materials to achieve a new result, which is repair of dead or damaged heart tissue. This result constitutes Appellant's pioneering invention, which is deserving of broad protection.

Regarding the Examiner's contention in the Final Rejection at the top of page 19, that, "Strauer et al. et al. [sic] and Deb et al. provide evidence that intravenous and intraluminal administration fail to deliver sufficient cells to the site of damage to achieve the required result," Appellant is at a loss to understand the relevance of such contention to the issue of breadth of the claims. Such lack of understanding is compounded by the Examiner's further statement that, "However, all these details are off-point to the issue of the breadth of the claims."

The Examiner further stated at page 19 of the Final Rejection:

> The claims merely recite intravenous or intraluminal administration, and do not provide any other limitations (e.g., which veins, which lumens, how many cells, any other substances administered, etc.). Therefore the breadth of the claims is very large, a factor which is to be taken into account when making the determination of whether or not the amount of experimentation required by the skilled artisan to practice the claimed invention in its full scope is or is not undue.

Addressing the above limitations is well within the capability of one skilled in the medical art, as evidenced by the Declarations of Drs. Heuser and Lorincz. Both Dr. Heuser and Dr. Lorincz are well aware of intraluminal and intravenous techniques by virtue of their education and professional experience. Thus, there is no mystery why these experts concluded that the description contained in Appellant's specification regarding enablement is sufficient to practice the invention defined in claims 248 and 249. Obviously, a skilled physician, as contrasted to a non-physician, would have little or no problem in using known administration techniques to inject known materials at an appropriate site in the body. One skilled in the art

would have no difficulty in selecting dosages as discussed more fully at pages 60-63 of this Brief. The Supplemental Declarations of Drs. Heuser and Lorincz, at Paragraph 8, attest to this situation. It is submitted that the Examiner is bound to accept the expert opinions of Drs. Heuser and Lorincz and is not permitted to substitute her opinion for that of the experts. The Examiner cannot ignore such experts' opinions that predictable results would be obtained. See In re Alton, supra.

One final point remains. The Court in Wands reversed the PTO's lack of enablement rejection concluding that the specification provided sufficient guidance and direction on how to carry out the claimed invention and presented examples. The Court also found that all the methods required for carrying out the invention were old and well known and that the level of skill in the requisite art was high. Appellant believes that this is "on fours" with the present factual situation where the level of skill is "admittedly high" and the claimed invention requires the use of old materials and old methods.

For the reasons stated above, Appellant submits that the Examiner's rejection of claims 248 and 249 for lack of enablement is erroneous and is not supported by the evidence discussed above. Accordingly, Appellant requests the Board to reverse this rejection.

Rejection of Claims 236, 238, 239, 243-253, and 256
Under 35 U.S.C. §112, first paragraph

Claims 236, 238, 239, 243-253, and 256 stand finally rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The Examiner's conclusion is that undue experimentation would have been required to make and use the claimed invention. In support of such conclusion, the Examiner apparently relied upon the factors set forth in Wands except no specific weight was assigned to the skill in the art. However, the Examiner provided

only argument, not any specific evidence, to support such conclusion. Further, the Examiner did not consider Appellant's evidence regarding enablement that was proffered in the Declarations of Drs. Heuser and Lorincz. Such lack of consideration is error and leads to the erroneous conclusions set forth in the Final Rejection.

Appellant believes, based upon the Examiner's remarks in the Final Rejection, that this rejection is predicated upon an erroneous reading of the subject matter of the claims. First, only claims 238 and 239 require repair of a dead/damaged portion of a heart. However, the Examiner appears to have treated all claims as though repair is required. This is error and leads to an incomplete treatment of the other claims. Second, it is evident that, as in the case of the co-pending appeal of Appellant's patent application, Serial No. 09/794,456, the Examiner has attempted to read the term "new artery" as limited to *"de novo* arteries." No such limitation appears in the claims or in the specification, and, accordingly, it is error to predicate the rejection in this manner. In summary, the Examiner has misconstrued the subject matter of the claims and has not treated the actual claimed subject matter. In view of such error, the Board is respectfully requested to reverse this rejection.

As pointed out above, Appellant believes that an identification of the skill level in the art is a critical factor because such level obviously impacts any meaningful analysis of the other Wands factors.

At the last line of page 25 of the Final Rejection, the Examiner stated that "the level of skill in the art is admittedly high." The level of skill is further amplified by the Examiner's recognition on page 25, lines 4-6 of the Final Rejection that medical professionals who practice in the field of the claimed invention, "must endure years of study and training before being certified to attempt such procedures on human patients." Drs. Heuser's and Lorincz's education,

training, and experience, clearly meet such high skill level, which further exacerbates the Examiner's erroneous failure to consider and weigh Appellant's declaration evidence with regard to the claimed invention's enablement.

Regarding the Wands factor involving quantity of experimentation required, the Examiner alleged, in the Final Rejection, that a very large amount of experimentation would be required to make and use the claimed invention and pointed to pages 1916-1918 of Strauer to support such allegation. One skilled in the medical art would readily recognize and determine how to select cell population, delivery means, and cell transplantation timing following a heart attack and recognize that Strauer performed little or no experimentation.

Such recognition and determination fall within the skill of the medical art and require no more than routine experimentation, as confirmed by the expert opinions in the Declarations of Drs. Heuser and Lorincz. Appellant submits that the Examiner has exaggerated the amount of experimentation required. Strauer did not report that a large amount of experimentation was conducted. To the contrary, Strauer selected a cell population that worked and did not report any cell populations that did not work. There is no evidence that these skilled medical practitioners required a large amount of experimentation, if any, in this regard. The Board's attention is further directed to the goals of Strauer regarding delivery means and the timing of cell transplantation. Strauer desired to select the "most efficient' application method and to select an "ideal" time point for delivery. Strauer's determination of the most efficient and ideal factors clearly do not rise to evidence of a large amount of experimentation.

The Examiner also stated at page 23 of the Final Rejection that, "despite all of this work, growth of new cardiac muscle was not achieved." While it is not clear what the Examiner meant by "this work," it is clear from page 1913 of Strauer that transplantation of autologous BMC's

improved cardiac function significantly and such, "marked therapeutic effect may be attributed to BMC-associated myocardial regeneration and neovascularization." Strauer's results are confirmed by Wollert, where new cardiac muscle and new arteries were grown in a human heart by BMC-associated transplantation. Wollert conducted a 60 patient randomized-controlled trial, which is universally recognized as the "gold standard" for clinical trials. In addition, Wollert utilized full color cardiac MRI images to document the improved functional recovery achieved in the BMC group of patients. The Deb study, which involved sex mismatched bone marrow transplants, incontrovertibly confirmed through autopsy proof that BMC's form new cardiac muscle in human hearts. The Examiner, at page 14, lines 15 and 16, admits that cardiomyocytes were formed by Deb. This admission is at odds with the Examiner's allegation. In any event, Deb performed <u>no</u> experimentation regarding how to achieve the claimed results.

Appellant points out that the Second Supplemental Declarations of Drs. Heuser and Lorincz, at paragraph 9, contain the opinion that one skilled in the medical arts, having read paragraphs 6-8 of the Second Supplemental Declaration, would be enabled to practice the claimed method and predictably anticipate the results defined therein without need for resorting to undue experimentation. The Examiner failed to address this strong, compelling evidence from highly skilled medical practitioners affirming enablement. Accordingly, there can be no question that no more than routine experimentation would be required to make and use the claimed invention.

Regarding the Wands factor of direction/guidance, in the Final Rejection, the Examiner alleged that the specification provides, "no guidance along the lines of the details worked out by Strauer et al." The appropriate test for enablement relates to the disclosed invention of Appellant, not Strauer. The fact that both Drs. Heuser and Lorincz find the details contained in

the instant specification to be enabling should be dispositive of this matter. There is no requirement that an applicant must anticipate the nature of future experimental work and then provide experimental details thereof in order to satisfy the enablement requirement. This is especially true when the future work is designed to improve or optimize the applicant's invention. All that is required is that an applicant provide sufficient detail to enable a skilled person in the art to make and use the claimed invention. The Summary of Invention portion of this Brief indicates where Appellant's specification has provided such detail by 1) describing in broad terms the method and manner for practicing the invention, 2) providing specific examples in the way of detail, and 3) supplying prophetic examples detailing how to practice the claimed invention.

In the Final Rejection, the Examiner gratuitously cited and partially discussed a variety of non-elected inventions in the topic of guidance. Appellant is uncertain why the Examiner wishes to potentially cast a cloud on such non-elected inventions by offering a premature and irrelevant "opinion" regarding such inventions. Appellant believes that such "opinions" are improper, inaccurate, do not appear to have been well researched, are potentially prejudicial to Appellant, and are obviously irrelevant to the claimed invention.

As noted in the preceding paragraph, the Examiner has improperly focused upon several non-elected inventions. In this context, the Board's attention is directed to the fact that the Examiner imposed a 94-way restriction requirement at the outset of prosecution. It appears to Appellant that the Examiner utilized an extremely narrow focus in determining that 94 separate and independent inventions were present in the claims of the instant application. As a result of such narrow focus, Appellant, a small entity, does not have the resources necessary to file and prosecute all of the remaining 93 inventions and thus likely will not obtain potentially valuable

patent assets. The Examiner's attempt at this time to "examine" the above-mentioned non-elected inventions, despite making the restriction requirement, is unwarranted and amounts to inconsistent and potentially prejudicial prosecution.

The Examiner, relying on Genentech Inc. v. Novo Nordisk A/S, (CAFC) 42 USPQ 2d 1001 (1997), asserted that, "The courts have also stated that "[t]ossing out the mere germ of an idea does not constitute an enabling disclosure...[R]easonable detail must be provided in order to enable members of the public to understand and carry out the invention." Appellant has demonstrated above at pages 51 and 52 of this Brief that the specification provides ample guidance to enable one skilled in the art to carry out and practice the claimed invention. Certainly, Drs. Heuser and Lorincz had no difficulty in reading and understanding the guidance set forth in the specification regarding making and using the claimed invention.

Regarding the Wands factor involving working examples, in the Final Rejection, the Examiner concluded that there are no working or prophetic examples directed to the elected invention. In support of such conclusion, the Examiner considered that even though prophetic examples were present, none of such examples are, "directed to administration of cells to grow cardiac muscle or a new artery." The Examiner appears to have overlooked Appellant's disclosure at page 46, lines 3-16, which contains a prophetic example of heart repair using cells to grow new muscle and new arteries wherein cells are seeded, "[I]mmediately adjacent to dead cardiac muscle." Note further that Dr. Heuser and Dr. Lorincz based their opinions, in part, on such disclosure. It was error for the Examiner not to assess the evidentiary weight of such disclosure.

It is well established that examples, whether working or prophetic in nature, are not required in an application. In the present case, the absence of a working example is of little consequence because the two Declarants believe that the specification is enabling.

Regarding the Wands factor involving complexity, the Examiner alleged, in the Final Rejection at page 25, that the invention is highly complex and pointed to all of the publications of record, especially Strauer, to support such allegation. The reason that Strauer does not support the Examiner's position has already been extensively discussed above, on pages 40-42 and 44 of this Brief, in connection with the prior enablement rejection for claims 248 and 249. The "other publications of record" are not identified or specifically addressed by the Examiner.

The Examiner further supports such allegation with a generalized statement that, "All inventions involving administration of active agents of any kind to a patient to achieve a physiological reaction are complex." Appellant submits that complexity must be considered in light of the context of the instant invention, rather than in a general sense. Appellant points out: 1) that all disclosed administration techniques were known in the art prior to the effective filing date of the application; and 2) that cells, including stem cells, along with associated preparation and handling techniques, were known in the art prior to the effective filing date of the application. What was not known or conceived by another was that, if cells were administered in accordance with the invention, new cardiac muscle and new arteries would be grown in a heart. This is Dr. Elia's novel and unobvious contribution to the medical art. The invention, once understood by one skilled in the art, is straightforward to practice, not complex, as alleged by the Examiner. Appellant recognizes that heart repair is a complex art; however, the skill level of the person working in this area is comparably high. For example, a skilled person in the medical art, such as Dr. Heuser, upon reading applicable portions of Appellant's specification, would be able

to practice the claimed method set forth without need for resorting to undue experimentation. In this regard, see the Second Supplement Declaration of Dr. Heuser. What may appear to be complicated to a layperson certainly would not be complicated to such highly trained and skilled persons.

Regarding the Wands factor involving state of the art, the Examiner, for the first time in the Final Rejection at page 25, cited two technical publications; namely, Balsam et al., 2004 Nature 428:668-673 and Ziegelhoeffer et al., 2004, Circulation Research 94:230-238, both of which bear a 2004 publication date. The Examiner asserted that the publications were probative evidence of the state of the art. Reliance upon such citations is misplaced because, as best understood by Appellant, the state of the art regarding enablement is that at the time of the filing of the instant application.

By citing the two new publications, the Examiner appears to be alleging that such publications are contradictory in that different theories relating to mechanisms for cardiomyocyte and artery formation have been reported by workers in the art. The correctness of any theory of artery formation advanced by these references is irrelevant to Appellant's disclosed and claimed invention. Whether new arteries are formed because of angiogenic factors released by the cells, by differentiation, or by another mechanism, is important from a scientific viewpoint but is not critical to Appellant's claimed method of stem cell implantation for growing new cardiac muscle and new arteries. The claims in issue neither recite nor require a particular theory of operation. It is axiomatic that an applicant is not required to disclose or claim a particular theory of invention in order to comply with the first paragraph of the statute. Both Balsam and Ziegelhoeffer conducted tests on murine models, not on a human patient. Accordingly, such

tests are deemed to be less relevant to the Examiner's new issue than those conducted on human patients by Strauer and Wollert.

The Examiner further alleges that Balsam is evidence that BMC's, "do not in fact, contribute to myocardial regeneration (i.e., growth of cardiac muscle)." The difference between Balsam's study and previous work is the nature of BMC's used. Balsam obtained whole bone marrow harvested from mice and then <u>isolated</u> several purified and highly purified subsets of cells, which is distinct from the whole bone marrow used by the other workers. Orlic, Strauer, Deb, and many others have repeatedly and independently reported BMC's can and do form new cardiomyocytes. Thus, the Examiner's attempted comparison based upon these publications is clearly invalid because different cellular materials were used in the respective publications. Balsam does not, in fact, support that the art is contradictory, and it is insufficient to establish a contradictory state of the art. Moreover, the autopsy proof of new cardiomyocyte formation in humans offered by Deb satisfies the "best evidence" rule in regard to this issue.

Additionally, the Examiner in the Final Rejection at page 25 stated that, "None of the numerous post-filing date publications put on record by Applicant to support enablement of the claimed invention report the *de novo* growth of an artery as defined by Applicant, including Strauer et al." The above quoted passage contains three errors. First of all, Appellant did not rely upon any publications, including Strauer, to support enablement of the claimed invention but instead relied on Strauer as demonstrating operability. Regarding the claimed invention's enablement, Appellant relies upon the instant specification, as well as the objective declaration evidence of Drs. Heuser and Lorincz. Even a cursory reading of the respective Declarations indicates that both Declarants relied solely upon identified portions of the specification and the current claims to conclude that enablement was present. Secondly, Strauer, Wollert, and Deb

confirm that new cardiac muscle and new arteries are grown in a human heart. Thus, the Examiner's statement is obviously erroneous. Moreover, Strauer and Wollert provide rebuttal evidence that heart repair (specified in claims 238 and 239) does, in fact, occur by practice of the claimed invention. Thirdly, no publications were relied on to show *de novo* growth of an artery. This is not surprising because such *de novo* artery terminology appears to be the Examiner's creation. The Examiner apparently mentioned Strauer in this regard. However, Strauer reports, at page 1913, the achievement of "neovascularization" but nowhere uses the term *de novo* artery.

By apparently predicating this enablement rejection upon whether the claims are limited to the formation of *de novo* arteries, the Examiner has again taken a position that is inconsistent with her examination during the prosecution of the Weiss patent application. The Board's attention is once more directed to the Weiss patent file history, which indicates that no enablement issue was raised regarding whether the term "new", as used by Weiss at column 12, lines 48-51 in connection with the *in vivo* formation of new dopamine neurons, was limited to *de novo* formation of such neurons. Like Appellant's application, the term *de novo* does not appear in the Weiss patent. Appellant's perusal of the Weiss patent indicates that any such rejection would have been unwarranted because it is clear from the balance of the Weiss patent specification that dopamine neurons were formed by the process of the invention and that "new" adequately describes such formed neurons. Likewise, Appellant has used the term "new" to describe the results of his invention, i.e., new cardiac muscle and new arteries, and has presented adequate description in the specification for those skilled in the art to understand the meaning of the term. Appellant submits that the above-mentioned fact situation indicates that the Examiner applied an erroneous and inconsistent examination standard to the instant application and that as a result, Appellant has been denied procedural due process.

By way of background, the term "new" was added to the claims following comments made by the Examiner's supervisor, Dr. Yvonne Eyler, during the January 6, 2004 interview to distinguish Appellant's heart repair method from the fused tissue obtained by Murry. Following such comments, Appellant's counsel stated that the claims would be amended to include the words "forming (or growing) new arteries" rather than "forming (or growing) arteries" and further pointed out that the specification supported such amendment. Appellant stated that such amendment would be made to more clearly define differences over Murry. Following the interview, Appellant believed that the three Examiners attending the interview (including Examiner Kemmerer) understood the meaning of the word "new" in the context of the invention. Obviously, Appellant was surprised when the Examiner raised the *de novo* artery issue.

Appellant believes that the word "new" speaks for itself when viewed in context of Appellant's specification and claims. As pointed out in the specification, Appellant forms new arteries and new cardiac muscle as a result of the inventive method. The Examiner is attempting to obscure the clear meaning of an ordinary word by suggesting that the artery "must be formed *de novo* and not merely repair, growth, or re-direction of an existing artery." The word "new" in the context of the invention simply means an artery that is newly formed or grown by Appellant's process. See the specification at page 44, line 19 to page 46, line 16; Example 19 at page 55, line 13 to page 57, line 3; and Example 36 at page 62, lines 1-10, as read with Example 18. In other words, the formed artery, following completion of the growth process, was not present in such form prior to conducting such process. Obviously, new tissue growth or formation is involved. The meaning of the phrase "growing a new artery" is thusly set forth above, despite the Examiner's highly improper attempt to redefine the word and then construe the claims to be limited to the Examiner's definition. It is the Examiner, not Appellant, that is

implying that the newly formed artery must involve "*de novo* growth of an artery." Such implication is clearly improper because it is incumbent upon an applicant, not an examiner, to provide terminology defining an invention. What was accomplished by the amendment was to make explicit what was implicit, i.e.; that a new artery was formed.

It is also pointed out that neither Dr. Heuser nor Dr. Lorincz had any difficulty understanding the claim limitation "growing a new artery" because both experts reached the conclusion that the disclosure enabled the subject matter of the claims. Thus, Appellant believes that the Examiner likewise should not have any difficulty understanding that the claims simply mean growing a new artery and that such growth is well understood by a skilled person in the medical art.

The claims are not limited to *de novo* artery formation because Appellant's specification and claims used the language "new" in describing the claimed invention. Moreover, the Examiner has not adequately defined the meaning of the term *de novo* as it relates to the formation of arteries nor has the Examiner proffered any evidence of the prior art's use of such term in regard to the formation of new arteries at the time of Appellant's invention. Under these circumstances, the Examiner's attempt to redefine and delimit the claimed invention is improper.

Appellant was not familiar with the terminology *de novo* arteries at the time the application was filed. Obviously, an applicant cannot be expected to be clairvoyant and use unfamiliar, later-developed terminology in describing and claiming an invention. It is error for the Examiner to create terminology defining Appellant's claimed invention; deem that the claims are, somehow, limited to such undefined terminology; and then make a rejection based upon such terminology and claim interpretation.

The claims, for reasons described above, are not limited to *de novo* formation of new arteries.

In summary, it is evident to Appellant that the Examiner improperly characterized the state of the art by relying upon the Balsam and Ziegelhoeffer publications, as well as fabricating an issue involving *de novo* arteries. Accordingly, the Examiner has presented no meaningful evidence in evaluating the state of the art that would support a finding of lack of enablement.

Regarding the Wands factor involving predictability, the Examiner alleged at page 26 of the Final Rejection that, "administering active agents to a living patient to achieve a physiological response" is unpredictable, citing Ex parte Hitzeman, 9 USPQ 2d 1821 (BPAI 1987); In re Fisher 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical co. Ltd., 927 F.2d 1200, 1212, 18 USPQ 2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). Such cases are inapposite because in those cases, unlike in the present case, no evidence regarding predictability was present. In any event, no nexus was provided by the Examiner to establish that such legal tenant would be applicable to the facts of the instant application.

Regarding the Wands factor involving the breadth of the claims, Appellant believes that the breadth is commensurate in scope with the pioneering nature of the invention. The Examiner has presented no prior art that causes Appellant to limit his claims further than those currently under examination; and therefore, Appellant is entitled to such breadth. In the Final Rejection, the Examiner, at page 26, stated that, "The elected invention is directed to a method of administering any type of cell to an undefined area of the body of a human patient to grow new cardiac muscle and a new artery (of any type or location)." Regarding the first point, page 45, lines 1-4 of the specification broadly describes administering, "a gene or other genetic material

into muscle at a desired site." More specifically, directions are given to those skilled in the art for selecting a desired site and include such factors as, "size, vascularity, simplicity of access, ease of exploitation, and any other desired factors." Page 46, lines 3-10 of the specification describes seeding immediately adjacent to dead cardiac muscle with appropriate cells, genes, or other genetic material. In addition, page 45, lines 19-21 describes injecting a genetic material (in this case, a gene) into cardiac muscle to form cardiac muscle and artery to revive or replace a dead portion of the heart. Such identified disclosure is commensurate in scope with the scope of protection sought for the claims and, obviously, is limited by the claimed results.

Appellant notes that the Examiner raised the issue of dosages in the summary of the Final Rejection, at page 26, lines 15-19, and connected such issue with the breadth of claims Wands factor. Examples 19 and 36 specifically describe dosages for intrasmuscular injection.

It would be a routine matter to apply proper dosages, via either intravenous or intraluminal administration, for at least several reasons.

Firstly, "... it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation. ...." MPEP Section 2164.01 (c).

Secondly, during the examination of the Weiss patent, the Examiner never raised the issue of dosages, either in the rejection or in the analysis of the Wands factors. Like the instant application, the Weiss patent did not describe a dosage range but rather described dosages at column 6, lines 19-27 as:

> An "effective amount" is an amount of a therapeutic agent sufficient to achieve the intended purpose. The effective amount of a given therapeutic agent will vary with factors such as the nature of the agent, the route of administration, the size and species of the animal to receive the therapeutic agent, and the purpose of the administration. The effective amount in each individual case

> may be determined empirically by a skilled artisan according to established methods in the art.

Both the Weiss patent and the instant application disclose specific dosages in their specifications, and their respective claims do not contain dosage limitations. However, unlike in the Weiss prosecution, in the instant prosecution, the Examiner adopted and applied a different enablement standard regarding dosages. Such inconsistent examination is improper because all applicants are entitled to the same administrative due process.

Thirdly, Appellant's specification describes new artery growth and heart repair by direct injection of growth factor cells in dosage ranging from approximately 6.25×10^6 (Example 36) to approximately 12.5×10^6 (Example 19). Available off-the-shelf cDNA clones (nucleic acids) are directly injected into either the cardiac muscle (Example 19) or the coronary artery (Example 36). Each example describes forming a new artery and repairing a damaged heart with increased coronary blood flow. Each example also discloses slowly injecting the growth factor to avoid any carry away. While these examples employ nucleic acids, one skilled in the art reading the specification, which teaches that cells, i.e., stem cells (BMC's) possess equivalent activity to genes (nucleic acids) and other genetic material, in forming a new artery and repairing a dead or damaged portion of a heart, would be able to easily extrapolate the number on a weight basis of mononuclear cells required to obtain equivalent results. Note in this regard that Strauer discloses injecting six (6) to seven (7) times with 1.5 to 4×10^6 cells without disclosing any difference in results over the entire dosage range. Therefore, there is no significant clinical difference between Appellant's 6.25 to 12.5×10^6 and Strauer's 9 to 28×10^6 dosage ranges. Further, such skilled person would understand that intravenous or intraluminal administration routes would generally require larger doses than the direct injection route of Examples 19 and 36, and, for

example, simply doubling the dosage to 12.5 to 25 x 10^6 cells would essentially encompass Strauer's entire range. It is clear from Strauer that there is no risk for over-dosing, particularly using autologous BMC's, which are contemplated in Appellant's specification.[2] cf. In re Bundy, 642 F. 2d 430, 434, 209 USPQ 48, 51-52 (CCPA 1981).

Fourthly, both Drs. Heuser and Lorincz have stated, in paragraph 8 of their respective Supplemental Declarations, that dosages are a matter of routine medical practice and then have enumerated various factors that skilled physicians routinely consider in this regard. Such Declarations raise a genuine issue of material fact that cannot be ignored by the Examiner in the analysis of this Wands factor.

The evidence proffered by Appellant in the above four paragraphs makes it clear that undue experimentation is not required to select an appropriate dosage in the practice of the claimed invention.

It is again pointed out that the Examiner, in the Final Rejection, made no comment on the record regarding the merits of the Second Supplemental Declarations of Drs. Heuser and Lorincz, which confirmed enablement of the claimed invention. The Examiner's failure to consider and evaluate the evidentiary value of the two expert opinions amounts to error for reasons already set forth in earlier portions of this Brief. See In re Alton, supra. If the Examiner takes issue with such Second Supplemental Declarations, it is incumbent upon her to explain her position. Drs. Heuser and Lorincz rendered opinions that the formation of new cardiac muscle

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[2] The conversion for dosages of nucleic acids to corresponding dosages of cells was conducted as follows. Examples 19 and 36 specified dosages of 500 micrograms (ug) and 250 ug, respectively. The weight of nucleic acids of an average cell was considered to equal 40 picograms (pg). The described dosages of 250 and 500 ug when converted to pg by multiplying by 10^6 equals 250 x 10^6 pg and 500 x 10^6 pg. Since nucleic acids of an average cell have an average weight of 40 pg, a conversion is made by dividing 250 x 10^6 and 500 x 10^6 by 40 to arrive at the equivalent cell dosages, which are 6.25 x 10^6 and 12.5 x10^6, respectively.

and new arteries was enabled. It was further error for the Examiner not to have weighed the probative value of such expert opinions during her analysis of the Wands factors.

As mentioned above, the Court in Wands reversed the PTO's lack of enablement rejection concluding that the specification provided sufficient guidance and direction on how to carry out the claimed invention and presented examples. The Court also found that all the methods required for carrying out the invention were old and well known and that the level of skill in the requisite art was high. Appellant believes that this is "on fours" with the present factual situation where the level of skill is admittedly high and the claimed invention requires the use of old materials and old methods. Appellant believes that the results described in prophetic Examples 19 and 36 discussed earlier on pages 31, 32, and 49 of this Brief, were confirmed by the work of Strauer, which used equivalent dosages of BMC's for heart repair and thus elevates the level of these prophetic examples to that of working examples. MPEP Section 2164.06.

The Examiner summarized this rejection at page 26 of the Final Rejection. Such summary paraphrases all the Wands factors, except for the factor involving a determination of the skill level in the art. Clearly, the skill level in the art impacts the evaluation of all of the Wands factors and should have been considered by the Examiner in this context. It is again noted that the Examiner's discussion regarding state of the art appears to have been predicated upon a lack of enablement for achieving *de novo* formation of an artery. Such aspect of the rejection is erroneous because the claims do not recite nor are they limited to the term *de novo* artery.

Appellant believes that the Examiner has failed to articulate adequate support for the rejection. Even assuming, *arguendo,* that the Examiner has made out an initial *prima facie* case of lack of enablement, In re Oetiker, supra., the Examiner has failed to adequately explain how

the Declarations of Drs. Heuser and Lorincz failed to overcome such a *prima facie* case. "A declaration … is, itself evidence that must be considered." See MPEP Section 2164.05. Appellant believes that these Declarations are sufficient to shift the burden of going forward with evidence back to the Examiner. It was error for the Examiner to determine patentability without considering the entire body of evidence in the record. In re Oetiker, at 1445, 24 USPQ 2d at 1444. Accordingly, Appellant requests the Board to reverse the Examiner's rejection of claims 236, 238, 239, 243-253, and 256.

Priority

The Examiner, in the section of the Office Action entitled "Priority", noted that the application, "appears to be virtually the same" as parent application 09/064,000 and fixed the effective date for the claimed invention as April 21, 1998, for purposes of applying prior art. The Examiner also stated that, "The instant application is also a continuation-in-part of 08/837,608, filed 21 April 1997; 08/326,857, filed 21 October 1994; 08/087,185, filed 02 July 1993; and 08/053,886, filed 27 April 1993."

However, the Examiner incorrectly concluded that, "none of these applications have support for the currently claimed invention, i.e., administration of cells to repair dead or damaged heart tissue." Further, the Examiner mischaracterized the disclosures of the '886, '185, and '857 applications as being, "limited to disclosures of dental implants and clearly do not provide support for treatment of non-dental tissues such as heart."

The disclosure found on page 20, line 10 through page 21, line 15 of the instant application relates back to parent application Serial No. 08/087,185 which bears a July 2, 1993 filing date and describes using angiogenic growth factors comprising living organisms, i.e. cells, for growing soft tissue in a body, such as tissue of mesodermal origin, by injecting the growth factor at a selected site in a patient. Official Notice should be taken of the fact that the term "soft tissue" is well known and understood by those skilled in the art to define tissues that connect, support, or surround organs or other structures of the body and include muscles, blood vessels, nerves, etc.[3] One skilled in the art would also understand that the growth factors described as multifactorial and non-specific in the July 2, 1993 application, i.e., characterized as being able to

[3] National Cancer Institute, Cancer Facts; Soft Tissue Sarcomas: Questions and Answers, What is Soft Tissue? http://cis.nci.nih.gov/fact/6_12.htm. A copy of information from such website has been provided for the readers' convenience and is attached hereto as Exhibit J.

control cell growth, migration, and function, are stem cells. Such disclosure clearly conveys to one skilled in the art that Appellant was in possession of the novel method of using cellular angiogenic growth factors (stem cells) to grow mesodermal tissue, which include blood vessels, i.e., arteries and cardiac muscle in human patients. Further, page 31, lines 18 - 26 describes injecting a growth factor into the body to cause the body "to grow, reproduce and replace leg bone, facial bone, and any other desired soft and hard tissue in the body", i.e., organ. The specification describes directly injecting living cells, e.g. stem cells, into a selected area in an organ to grow, reproduce, and replace desired tissue. While it is true that the word "heart" does not appear, Appellant believes that one skilled in the art would understand that organs such as the heart and arteries are comprised of soft tissue of mesodermal origin. Those skilled in the art reading such disclosure would understand that to "grow, reproduce and replace" soft tissue organs would include using multifactorial and non-specific cellular growth factors, i.e. stem cells, to affect angiogenesis and growth of new tissue/organ of mesodermal origin, including arteries and muscle such as those found in the heart. Appellant believes that the aforesaid teachings evince possession of the novel concept of injecting cells directly, systemically, in a carrier or by any other desired method to grow, reproduce, or replace hard or soft tissue organs as early as the July 2, 1993 filing date of Appellant's parent application Serial No. 08/087,185.

Appellant believes that the above-identified disclosures found at pages 20, 21, and 31 of the instant application, which correspond to disclosures carried forward from parent applications in the chain of co-pending applications relied upon under 35 U.S.C. §120, teach the manner and process of making and using the invention which correspond in scope to the subject matter of the newly submitted claims and thusly satisfy both the description and enablement requirements of 35 U.S.C. §112. Accordingly, Appellant claims the benefit under 35 U.S.C. §120.

While Appellant maintains that the present invention is entitled to the benefit under 35 U.S.C. §120, at the same time Appellant recognizes that there is no issue on appeal relating to priority. Such issue is rendered moot due to Appellant's cancellation of claims 254 and 255.

CONCLUSION AND RELIEF SOUGHT

Reversal of the Final Rejection of claims 236, 238, 239, 243-253, and 256 and an indication of the patentability of said claims over the rejections of record is respectfully requested.

Respectfully submitted,

Dated: 06/09/05

Gerald K. White
Gerald K. White
Reg. No. 26,611
Attorney for Appellant

Dated: 06/09/05

Charles N. Lovell
Charles N. Lovell
Reg. No. 38,01
Attorney for Appellant

GERALD K. WHITE & ASSOCIATES, P.C.
205 W. Randolph Street
Suite 835
Chicago, IL 60606
Phone: (312) 920-0588
Fax: (312) 920-0580
Email: gkwpatlaw@aol.com

APPENDIX

Claims on Appeal

Exhibits

Exhibit A	Google search, http:// www.meta-library.net/bioglosss/stemcel-body.htm
Exhibit B	Publication, "Tubes, Branches, and Pillars," American Heart Association
Exhibit C	Website information, Nathan Bahary, M.D., Ph.D., http://www.mgb.pitt.edu/personnnel/Bahary_Nathan.htm
Exhibit D	Weiss U.S. Patent No. 6,844,312
Exhibit E	Publication, "Milestones in the Development of Pediatric Hematopoietic Stem Cell transplantation – 50 Years of Progress", Pediatric Transplantation
Exhibit F	Publication, Automated Isolation of Mononuclear cells, www.ncbi.nlm.nih.gov
Exhibit G	Publication, Human bone marrow processing, www.ncbi.nlm.nih.gov
Exhibit H	Publication, Use of the Terumo SteriCell, www.ncbi.nlm.nih.gov
Exhibit I	Third Supplemental Declaration of Richard Heuser, M.D., F.A.C.C., F.A.C.P., dated 02/15/05
Exhibit J	Publication, Cancer Facts; Soft Tissue Sarcomas: Questions and Answers, What is Soft Tissue? http://cis.nci.nih.gov/fact/6 12.htm

CLAIMS ON APPEAL

Claim 236	A method of growing a new portion of a pre-existing heart comprising the steps of placing a growth factor in a body of a human patient and growing new cardiac muscle and growing a new artery in said heart.
Claim 238	The method of claim 237, further comprising repairing a dead portion of said heart.
Claim 239	The method of claim 237, further comprising repairing a damaged portion of said heart.
Claim 243	The method of claim 237, wherein said growth factor comprises a member selected from the group consisting of cells, cellular products, and derivatives of cellular products.
Claim 244	The method of claim 243, wherein said growth factor comprises a cell.
Claim 245	The method of claim 244, wherein said cell is multifactorial and non-specific.
Claim 246	The method of claim 245, wherein said cell comprises a stem cell.
Claim 247	The method of claim 236, wherein said growth factor is placed in said patient by injection.

Claim 248	The method of claim 247, wherein said injection is intravenous.
Claim 249	The method of claim 247, wherein said injection is intraluminal.
Claim 250	The method of claim 247, wherein said injection is intramuscular.
Claim 251	The method of claim 236, wherein said growth factor is placed in said patient by a carrier.
Claim 252	The method of claim 251, wherein said carrier comprises an angioplasty balloon.
Claim 253	The method of claim 236, wherein said growth factor comprises a gene and a cell.
Claim 256*	The method of claim 255, wherein said new muscle comprises cardiac muscle and said growth factor comprises a stem cell.

* Claim 256, in independent form, would read as follows:

A method of growing a new portion of a pre-existing heart comprising placing a stem cell in a body of a patient to grow new cardiac muscle in said heart.

Stem Cells

Stem cells are essentially undifferentiated cells. There are many kinds of stem cells, some more differentiated than others. When they divide, their progeny mature and specialize into a specific type of cell (i.e. heart, blood, liver). These differentiated cells form an embryo. Stem cells also exist in adults (Adult Stem (AS) cells) and are used to repair and regenerate damaged organs and tissues throughout life. However, in adults the repair and regeneration by stem cells is limited to only certain cell types. In contrast, embryonic stem (ES) cells are not limited in there potential to differentiate into every cell type. Embryonic germ (EG) cells have the same potential as ES cells. It is the versatility and nonspecifically of these cells that gives them the potential to have therapeutic applications.

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Circulation Research

(*Circulation Research.* 2001;89:645.)

Editorials

Tubes, Branches, and Pillars

The Many Ways of Forming a New Vasculature

Hellmut G. Augustin

From the Department of Vascular Biology & Angiogenesis Research, Tumor Biology Center, Freiburg, Germany.

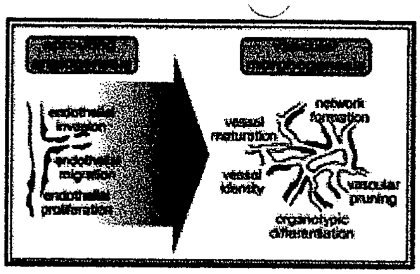
Correspondence to Hellmut G. Augustin, DVM, PhD, Department of Vascular Biology & Angiogenesis Research, Tumor Biology Center, Breisacher Str. 117, D-79108 Freiburg, Germany. E-mail augustin@angiogenese.de

Key Words: angiogenesis • vasculogenesis • intussusception • intussusceptive microvascular growth

The angiogenic cascade is getting increasingly complex. A few years ago, vasculogenesis and angiogenesis were considered as the primary mechanisms leading to the formation of new blood vessels. The original definition of vasculogenesis denotes the formation of a primary embryonic vascular network from in situ differentiating angioblastic cells.[1] In contrast, angiogenesis primarily referred to the sprouting of blood vessels from preexisting vessels.[1]

Recent advances in the identification of molecules that regulate angiogenesis and vascular remodeling have shown that the simplistic model of an invading capillary sprout is not sufficient to appreciate the whole spectrum of morphogenic events that are required to form a neovascular network (Figure 1).[1–3] Undoubtedly, vascular endothelial growth factor (VEGF) acts at an early point in the hierarchical order of morphogenic events and probably fulfills all criteria to be considered as a master switch of the angiogenic cascade. In contrast, the angiopoietins and their receptor Tie-2 as well as the ephrins and their corresponding Eph receptors appear to act at a somewhat later stage of neovessel formation. These molecules orchestrate a number of related, yet functionally and molecularly not well understood, processes such as vessel assembly (network formation and formation of anastomoses), vessel maturation (recruitment of mural cells [pericytes and smooth muscle cells], and extracellular matrix assembly, pruning of the primary vascular bed), and acquisition of vessel identity (formation of arteries, capillaries, and veins)[3,4] (Figure 2). Lastly, the mechanisms of organotypic differentiation of the vascular tree (continuous endothelium, discontinuous endothelium, fenestrated endothelium) are not at all understood and the first molecules that govern subpopulation-specific vascular growth and differentiation are just being uncovered.[5,6]

Figure 1. Change of paradigm. From sprouting angiogenesis to vascular morphogenesis. Basement membrane degradation, directed endothelial cell migration, and proliferation (left) were considered as the primary



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mechanisms of angiogenesis. Corresponding in vitro assays have greatly helped to uncover molecules and mechanisms of angiogenesis. Today, the complexity of the sequential processes leading to the formation of a mature vascular network is increasingly recognized. These involve mechanisms of vessel assembly (network formation and formation of anastomoses), vessel maturation (pericyte recruitment, extracellular matrix assembly, pruning of neovasculature), acquisition of vessel identity (arteries, capillaries, veins), and organotypic differentiation (continuous endothelia, discontinuous endothelia, fenestrated endothelia). Yet, experimental systems to study these steps are largely missing.

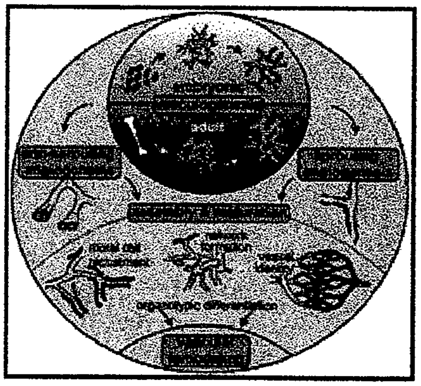

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Figure 2. Hierarchical order of morphogenic events during embryonic and adult growth of blood vessels. The primary formation of blood vessels occurs through mechanisms of vasculogenesis (center top). Vasculogenesis refers to the formation of a vascular network from precursor cells (angioblasts). Embryonic vasculogenesis results from the in situ coalescence of mesodermal angioblastic cells to form a capillary plexus. In contrast, adult vasculogenesis is mechanistically different and is mediated by the distal recruitment of angioblastic cells from precursor cell compartments (bone marrow). The secondary level of vascular morphogenesis describes the angiogenic formation of blood vessels. Angiogenesis refers to the formation of vessels and vascular networks from preexisting vascular structures (top, outer compartment). This can occur through classical sprouting angiogenesis with formation of anastomoses (top right) or through mechanisms of nonsprouting angiogenesis (top left). Nonsprouting angiogenesis occurs through mechanisms of intussusceptive microvascular growth (IMG) focally inserting a tissue pillar or by longitudinal fold-like splitting of a vessel. Sprouting angiogenesis and intussusception contribute to an increasing complexity of a growing vascular network. The network assembles and matures, eventually allowing directional blood flow. Cellular and biomechanical factors appear to be involved in shaping vascular identity (ie, arteries, capillaries, and veins), although there is also developmental biological evidence indicating that arteriovenous fate determination may occur before the formation of arteries and veins. Lastly, microenvironmental cues (extracellular matrix, cell contacts, and organ-selective growth factors) regulate the organotypic differentiation of a neovascular tree with continuous, discontinuous, and fenestrated endothelia. In contrast to the formation and maturation of new blood vessels through vasculogenic and angiogenic mechanisms, vascular remodeling describes the adaptational reorganization of an existing mature vasculature. This may occur acutely (eg, after sudden ischemia) or as a response to chronic stimuli (eg, atherosclerotic changes of vessel wall or in response to hypertensive biomechanical forces). The term "arteriogenesis" has been coined to describe the formation of collaterals from a preexisting capillary network after sudden ischemia as it occurs after cardiac ischemia or experimentally during surgically induced hindlimb ischemia. This process describes an adaptational remodeling phenomenon and should not be confused with the developmental acquisition of vessel identity that is associated with the formation of arteries, capillaries, and veins. Likewise, vessel cooption[18] describes a vascular remodeling phenomenon originating from an existing vasculature that may contribute to tumor vascularization.

The function of these molecules has largely been elucidated through genetic experiments in mice ablating or overexpressing individual molecules. Yet, a detailed understanding of their molecular and functional mode of action is missing, which is primarily due to the lack of appropriate in vivo and in vitro models in which to functionally study these molecules. Most in

vitro assays have very reductionist readouts such as endothelial cell chemoinvasion, migration, or proliferation. These assays have proven powerful in the early days of angiogenesis research. Yet, they are of limited use for the study of complex cellular interaction phenomena as they are associated with vessel assembly and vessel maturation. Likewise, most in vivo assays are either not quantitative or they are restricted to endpoint readouts that do not allow an appreciation of the dynamic three-dimensional spatiotemporal order of angiogenic processes, eg, in tumor models or in cardiac ischemia models. Most importantly, when it comes to studying angiogenesis in vivo, few laboratories apply three-dimensional techniques such as intravital microscopy or corrosion casting techniques to assess a neovascular bed. Instead, two-dimensional histological techniques are widely used to analyze angiogenesis in vivo. In fact, the counting of immunohistochemically stained microvessels in tissue specimens including tumors has become the gold standard to assess a neovascular bed in a given tissue.[7] Clearly, this reductionist analytical approach is by no means sufficient to realistically reflect the whole spectrum of three-dimensional morphogenic events dynamically over time.

It is primarily a consequence of the limited availability of appropriate experimental models and analytical tools that vascular network formation through the process of intussusception is still not widely appreciated. Intussusception or intussusceptive microvascular growth (IMG) describes the formation of a vascular network from an endothelial cell–lined vessel by focally inserting a tissue pillar or by longitudinal fold-like splitting of a vessel. As a consequence, IMG can result in complex vascular networks by a nonsprouting angiogenesis mechanism.[1,2]

The concept of vascular network formation through IMG is not new. Originally described more than 50 years ago,[8] analytical work on IMG was pioneered in the late 1980s and early 1990s by the Swiss anatomist Dr P.H. Burri.[9,10] This early work has clearly shown that IMG is an important nonsprouting angiogenesis mechanism that contributes to capillary network formation independent of classical sprouting angiogenesis (Figure 2). Physiologically, IMG occurs in a number of embryonic and adult tissues, most notably during embryonic vascularization of the lungs[11] as well as during the cyclic changes of the endometrial vasculature in the adult.[12]

In two studies published in this issue of *Circulation Research*, Dr Patan and colleagues[13,14] have shed further light into the complexity of intussusceptive microvascular growth. They have used the isolated mouse ovarian pedicle model to study IMG during wound healing–like granulation tissue formation and during growth of tumors grafted onto the ovarian pedicle. In this model, the ovarian vascular supply is surgically manipulated so that the isolated ovary is at the end of a pedicle that is supplied by the ovarian artery and the ovarian vein. This model was originally developed to perform hemodynamic studies in an experimental tumor that is supplied by a single feeding artery and a single collecting vein.[15] Patan et al have used this model to characterize the intussusceptive morphogenic remodeling of the ovarian vein and artery feeding into the granulation tissue[13] as well as into LS174T human colon adenocarcinoma growing in the isolated pedicle.[14] A zone of several millimeters was analyzed in both models through a carefully performed rather meticulous morphological analysis of several thousands of 2-µm serial sections. Computer-aided image analysis was then applied to three dimensionally reconstruct the vascular network. The results of both studies show quite clearly that IMG can lead to complex vascular networks completely independent of sprouting angiogenesis. Furthermore, the authors' high-resolution approach demonstrates how intussusceptive vascular folds organize to establish compound loop systems resulting from tissue segmentation and intussusceptive anastomoses.

As with any intriguing study, the experiments by Patan et al raise numerous additional questions. For example, what are the driving forces behind IMG? There is some evidence that the angiopoietin/Tie-2 ligand/receptor system is involved in controlling IMG.[16,17] Likewise, biomechanical forces may be involved in regulating IMG. The surgical manipulation in the ovarian pedicle procedure used by Patan et al[13,14] leads to significant changes in hemodynamic forces that may be involved in remodeling the preexisting ovarian vein as much as hemodynamic forces are believed to act as critical regulators of collateral formation following cardiac ischemia (arteriogenic vascular remodeling). This also raises the question of a zonal analysis of the observed intussusceptive morphogenic events, ie, does IMG occur in the center or in the periphery of the analyzed granulation tissue[13] and tumors?[14] Zonal analyses of vascular morphogenic processes are particularly relevant in the context of tumor angiogenesis. Microvessel counting studies usually quantitate intratumoral microvessel densities. Yet, the tumor periphery marks the invasive zone of a tumor and gives rise to metastatic cell dissemination. Thus, the equilibrium between tumor angiogenesis and remodeling of the preexisting vasculature in the tumor periphery (vessel cooption)[18] may be

very relevant in determining tumor fate. Lastly, and possibly most important, what is the quantitative contribution of IMG (and the other mechanisms of vessel formation) to neovascularization and particularly to tumor vascularization?

It is increasingly recognized that vascular morphogenesis is a complex process driven by a number of different mechanisms that can lead to the formation of endothelial cell–lined blood vessels. Figure 2 summarizes the hierarchical order of our present understanding of hemangiogenic morphogenic events (as opposed to lymphangiogenic processes). Future work in the field of angiogenesis research will need additional tools and models to systematically analyze angiogenic processes to fully understand the complexity of the angiogenic cascade. This will also include the implementation of more sophisticated invasive and noninvasive techniques to analyze the vasculature of human tumors. The elegant, yet cumbersome experimental, approach taken by Patan et al[13,14] clearly reflects our limited ability to appreciate angiogenesis as a dynamic three-dimensional process. The implementation of analytical techniques that systematically assess human tumor angiogenesis beyond the counting of microvessel densities is just at its beginning.[19] At the same time, novel angiogenic factors with a narrow cell and organ selectivity are being identified as inducers and modifiers of the angiogenic cascade.[5,6] Collectively, these observations indicate that the angiogenic cascade is far from being understood. Yet, a thorough understanding of the mechanisms of vascular morphogenesis will be a requisite for the rational translation of this knowledge into clinical application.

Footnotes

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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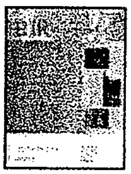

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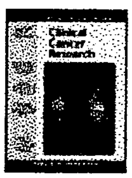

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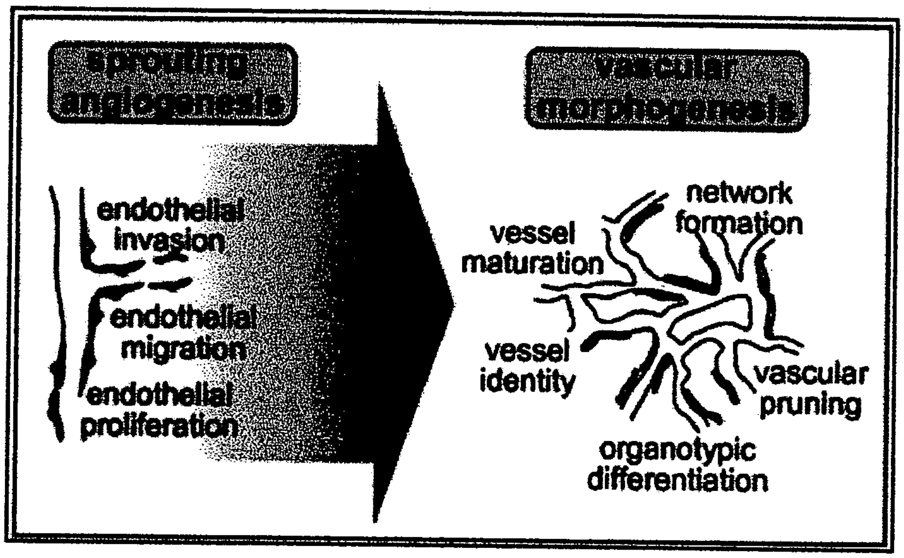

Figure 1. Change of paradigm. From sprouting angiogenesis to vascular morphogenesis. Basement membrane degradation, directed endothelial cell migration, and proliferation (left) were considered as the primary mechanisms of angiogenesis. Corresponding in vitro assays have greatly helped to uncover molecules and mechanisms of angiogenesis. Today, the complexity of the sequential processes leading to the formation of a mature vascular network is increasingly recognized. These involve mechanisms of vessel assembly (network formation and formation of anastomoses), vessel maturation (pericyte recruitment, extracellular matrix assembly, pruning of neovasculature), acquisition of vessel identity (arteries, capillaries, veins), and organotypic differentiation (continuous endothelia, discontinuous endothelia, fenestrated endothelia). Yet, experimental systems to study these steps are largely missing.

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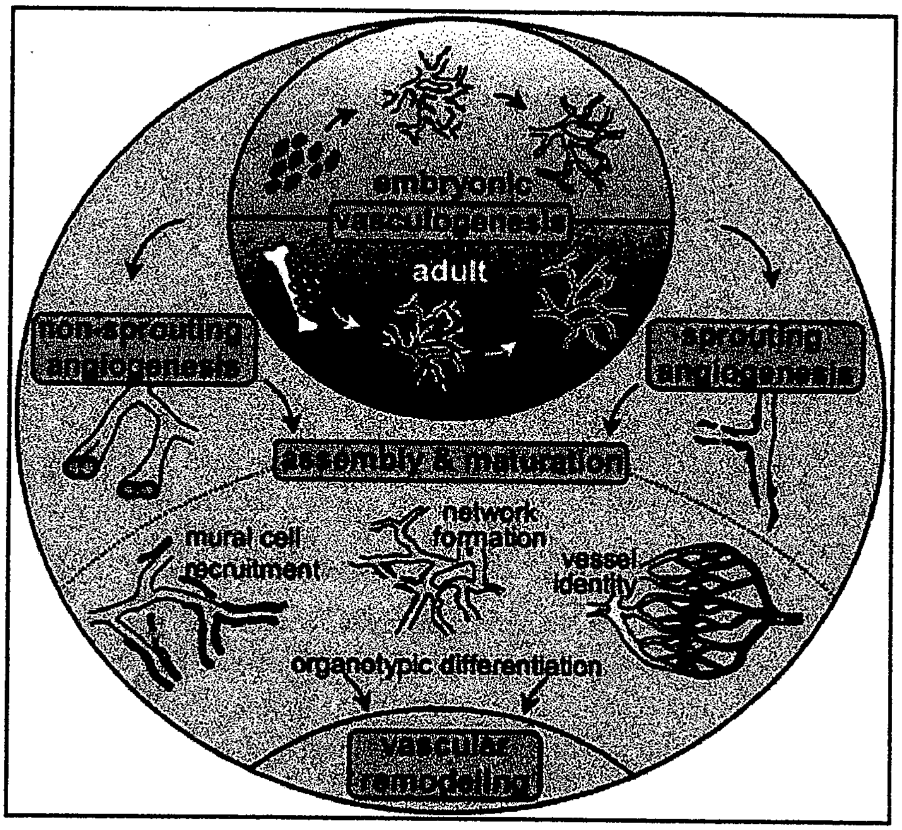

Figure 2. Hierarchical order of morphogenic events during embryonic and adult growth of blood vessels. The primary formation of blood vessels occurs through mechanisms of vasculogenesis (center top). Vasculogenesis refers to the formation of a vascular network from precursor cells (angioblasts). Embryonic vasculogenesis results from the in situ coalescence of mesodermal angioblastic cells to form a capillary plexus. In contrast, adult vasculogenesis is mechanistically different and is mediated by the distal recruitment of angioblastic cells from precursor cell compartments (bone marrow). The secondary level of vascular morphogenesis describes the angiogenic formation of blood vessels. Angiogenesis refers to the formation of vessels and vascular networks from preexisting vascular structures (top, outer compartment). This can occur through classical sprouting angiogenesis with formation of anastomoses (top right) or through mechanisms of nonsprouting angiogenesis (top left). Nonsprouting angiogenesis occurs through mechanisms of intussusceptive microvascular growth (IMG) focally inserting a tissue pillar or by longitudinal fold-like splitting of a vessel. Sprouting angiogenesis and intussusception contribute to an increasing complexity of a growing vascular network. The network assembles and matures, eventually allowing directional blood flow. Cellular and biomechanical factors appear to be involved in shaping vascular identity (ie, arteries, capillaries, and veins), although there is also developmental biological evidence indicating that arteriovenous fate determination may occur before the formation of arteries and veins. Lastly, microenvironmental cues (extracellular matrix, cell contacts, and organ-selective growth factors) regulate the organotypic differentiation of a neovascular tree with continuous, discontinuous, and fenestrated endothelia. In contrast to the formation and maturation of new blood vessels through vasculogenic and angiogenic mechanisms, vascular remodeling describes the adaptational reorganization of an existing mature vasculature. This may occur acutely (eg, after sudden ischemia) or as a response to chronic stimuli (eg, atherosclerotic changes of vessel wall or in

response to hypertensive biomechanical forces). The term "arteriogenesis" has been coined to describe the formation of collaterals from a preexisting capillary network after sudden ischemia as it occurs after cardiac ischemia or experimentally during surgically induced hindlimb ischemia. This process describes an adaptational remodeling phenomenon and should not be confused with the developmental acquisition of vessel identity that is associated with the formation of arteries, capillaries, and veins. Likewise, vessel cooption[18] describes a vascular remodeling phenomenon originating from an existing vasculature that may contribute to tumor vascularization.

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DEPARTMENT OF MOLECULAR GENETICS AND BIOCHEMISTRY

University of Pittsburgh, School of Medicine
Pittsburgh, PA

Bahary, Nathan

Nathan Bahary, M.D., Ph.D

Dept. of Molecular Genetics & Biochemistry
University of Pittsburgh School of Medicine
200 Lothrop Street
Office Location: BSTWR W1257
Lab Location: BSTWR W1207 & W1208
Pittsburgh, PA 15261
Office Telephone #412-648-3805
Lab Telephone #412-648-3159 (W1207)
Lab Telephone #412-648-3157 (W1208)
Email: bahary@pitt.edu
Website: (if any)

The principal theme of my research interests is to combine the power and insight of vertebrate development to elucidate basic molecular processes. Many of the genes involved in normal vertebrate development processes have been implicated in the causative pathway of human diseases. Thus, an understanding of normal developmental processes can be a key initial step toward fundamental advances in understanding and treating human disease. One of the methods used to characterize the discrete steps involved in normal vertebrate development is the generation of mutants and alteration of specific gene expression. In this regard, the zebrafish (Danio rerio) is an especially robust vertebrate system for isolating and defining the novel factors affecting these processes. The developing embryos are transparent, facilitating visualization, and have functioning organ systems by 24 hours post fertilization. Mutagenesis screens have

defined many ENU (which induces point mutations in DNA), gamma and insertional mutants whose defective gene functions can be described and investigated by many techniques, and isolated by genetic means.

My lab is focused on utilizing functional genomics and forward genetic screens in the zebrafish to help delineate basic aspects of vasculogenesis, hematopoiesis and gastrointestinal development and reaction of these tissues to injury. For instance, the zebrafish mutant *cloche* has a combination of hematopoietic, vascular and lymphoid defects which suggest that the *cloche* gene product is critical to the function of the hemangioblast. Characterizing and cloning this mutation will facilitate unique insights into the genetic cascade that regulates hematopoiesis and vasculogenesis.

In contrast to our depth of knowledge into various aspects of hematopoiesis and vasculogenesis there is a poor understanding on a molecular level of epithelial (including gastrointestinal) development/regeneration and gastrointestinal tumors. This paucity of knowledge has paralleled the lack of insight into the specific steps involved in the normal differentiation and patterning of the gastrointestinal system needed to base our understanding of the disease states. In my lab, transgenic zebrafish, made by fusing the promoter elements of gastrointestinal specific genes with a fluorescent marker (GFP) are being made to help elucidate the key steps in gastrointestinal development. Additionally, in-situ hybridization of genes from specific cDNA libraries is being done to analyze their temporal-spatial expression. Using a variety of techniques available in the zebrafish, such as over/misimpression, morpholino antisense RNA knockdown and the development of new transgenics, the normal function of these genes, and their possible roles in disease states can be elucidated. ENU mutagenesis in the zebrafish is also being utilized to screen for zebrafish with mutations in gastrointestinal development. Zebrafish harboring these mutations can be identified by loss of GFP expression in the transgenic fish, or by in-situ hybridization and morphology in non-transgenics.

Together, this work will help elucidate the pathways involved in normal hematopoiesis, vasculogenesis and gastrointestinal development with the

emphasis on providing the basis for designing rational, molecularly based disease directed therapies.

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Department of Molecular Genetics and Biochemistry
E1240 BSTWR
University of Pittsburgh
1-412-648-9570

MGB Webmaster
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Milestones in the development of pediatric hematopoietic stem cell transplantation—50 years of progress

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Abstract: In the 1950s, the first infusions of hematopoietic stem cells were given as a form of treatment for childhood leukemia. This heralded the beginning of a field that has expanded to include the treatment of immune deficiencies, a variety of leukemias and solid tumors, and then genetic diseases. A number of milestones are highlighted, particularly in regard to the use of alternative sources of hematopoietic stem cells such as unrelated donors, peripheral blood stem cells and umbilical cord stem cells. In addition, newer techniques of using non-myeloablative preparative regimens helped to reduce the toxicity and long-term consequences of hematopoietic stem cell transplant. Many diseases now benefit from the replacement of the marrow stem cells and the provision of a new immune system and improved immune surveillance.

Michael E. Trigg

Department of Pediatrics, Division of Blood & Bone Marrow Transplantation, A. I. duPont Hospital for Children, Wilmington, Delaware; Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania, USA

Key words: stem cell transplantation – pediatrics – blood formation

Michael E. Trigg, MD, Professor of Pediatrics, Jefferson Medical College, Chief, Division of Blood & Bone Marrow Transplantation, Department of Pediatrics, Alfred I. duPont Hospital for Children, 1600 Rockland Road, Wilmington, DE 19803, USA
Tel.: +1-302-651-5565
Fax: +1-302-651-5575
E-mail: mtrigg@nemours.org

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With the development of the age of atomic energy and interest in radiation, there developed an appreciation of the potential harm of radiation and the side-effects of exposing those in the industry to its effects, as well as the consequences of using atomic weapons. With this came an interest in understanding sensitivity to radiation and an appreciation for the hematopoietic toxicity it caused (1). In 1955–56, it was shown that mice could be protected from the lethal effects of total body irradiation with an infusion of allogeneic marrow, and in fact mice given an allogeneic marrow infusion could subsequently permanently accept a skin graft from the same marrow donor (2–4). These and other experiments showed clearly the radiation protective effect of transferring-in new cells and the development of a form of long-term chimerism and tolerance (5–10).

Abbreviations: ALL, acute lymphocytic leukemia; DLI, delayed lymphocyte infusions.

In this brief report, a number of milestones will be highlighted from the development of our current knowledge base in the field of pediatric hematopoietic stem cell transplantation (Table 1). Even the words 'hematopoietic stem cell transplantation' have evolved over time. Most work in this field of blood formation began using bone marrow. Blood as a source of peripheral stem cells was used with syngeneic transplants during the 1950s and 1960s (11, 12). However, our appreciation of the value of peripheral blood stem cells did not come about until the late 1980s and early 1990s (13). In the 1970s, the use of fetal liver tissue as a source of hematopoietic stem cells was investigated and applied in children with immune deficiencies (14). Early in their development, hematopoietic stem cells migrate from the yolk sack to the liver and temporarily make a home there before migrating to the spleen and bone marrow. Since that time in the 1980s, umbilical cord blood has been utilized as a source of hematopoietic stem cells. Motivated by the high concentration of these

Table 1. Milestones in pediatric hematopoietic stem cell transplantation

1	Experimental work
2	Initial work with children
3	Immune deficiencies
4	Selection of patients
5	Acute myelogenous leukemias
6	Neuroblastoma
7	Adding donors
8	Peripheral stem cell transplants
9	Cord blood transplants
10	Genetic diseases
11	Non-myeloablative transplants
12	Conclusions

cells during fetal development and soon after birth, the use of stem cells have been expanded *in vitro* and also been used for transplant purposes (15). More recently, the words 'stem cells' have taken on a new meaning because they describe cells which are usually obtained from early blastocysts or embryos. These cells have the capability of forming tissues or, in some cases, a whole living being. Thus, pediatric marrow transplantation has taken on new meaning and the sources of these hematopoietic stem cells have been expanded. This accounts for the change in name from pediatric marrow transplantation to pediatric hematopoietic stem cell transplantation.

Experimental work

Out of the atomic age and the atomic bomb experience came the work of the late 1940s and 1950s on protection from the hematologic effects of irradiation (16). A number of animal models were developed, and from this came the understanding that infusions of allogeneic marrow from inbred strains of mice could protect allogeneic irradiated mice (4, 8, 9). Infusions of marrow from related mice could also induce a tolerance to skin grafts (5). This led the way to an understanding of the cellular protective effects of infusions of marrow in otherwise irradiated individuals.

Initial work with children

In the 1950s, Thomas and others published their groundbreaking experience with infusions of syngeneic marrow into twins with leukemia who had been treated with supralethal doses of total body irradiation (12, 16). The prompt hematologic recovery and well being of these children against more than twice the lethal dose of irradiation attested to the protective effects of the marrow. However, these experiments took place during the initial phases of transplantation and also during the time of our initial leukemia trials, as we tried to understand how best to treat that disease. The role of continuation and maintenance chemotherapy in the treatment of childhood leukemias was not understood at all, nor were there very many chemotherapeutic agents from which to choose. As a result, by current standards these children were inadequately treated for their underlying leukemia and unfortunately had a subsequent recurrence of their underlying disease. This experience does not speak to a failure of transplantation but rather to a failure of our understanding of how to best treat leukemia back in the 1950s. It speaks to the fact that infusions of hematopoietic stem cells can provide a protective effect from the hematopoietic-suppressive effects of total body irradiation (17).

Soon after this, work began in closely related dog litter mates and this provided us with a sound scientific basis for most, if not all, of the future work to come out of the Seattle bone marrow transplant group and other groups around the world (7, 10).

Immune deficiencies

In the 1960s, a group from Minnesota used tissue typing to select a sibling marrow donor for a child with severe combined immune deficiency (14). The infusion of marrow provided immunologic recovery for this child, who is currently alive and in his 30s (14). Again, this milestone in the development of pediatric hematopoietic stem cell transplantation provided a basis for large numbers of transplants for children with a variety of immune deficiencies and set the stage for utilizing hematopoietic stem cell transplants to correct the hematopoietic and immunologic deficiencies induced by large doses of chemotherapy and radiation that are employed to treat underlying malignancies (18, 19). Although a number of other cellular and humoral factors have been utilized to treat immune deficiencies, none have been as successful as the use of hematopoietic stem cells (14, 20). Although the first child to receive such a transplant had severe combined immune deficiency and required no preparative therapy, our understanding of these many immune deficiencies has increased over time to include a realisation that some of these children require immune suppression or ablation in order to make room for a new graft or to prevent stem cell graft rejection (21). These techniques, of making a space for new stem cells resulted, in some cases, in incomplete engraftment or in

Table 2. Indications for bone marrow transplantation

Malignant disorders	Non-malignant disorders
Leukemia	Bone marrow failure syndromes
Acute myeloblastic leukemia	Acquired severe aplastic anemia
Acute lymphoblastic leukemia	Fanconi's aplastic anemia
Chronic myelogenous leukemia (adult type)	Reticular dysgenesis
Chronic myelogenous leukemia (juvenile type)	
Myelodysplastic syndromes	Immunodeficiency states
Acute myelofibrosis	Severe combined immunodeficiency disease
Some less severe combined immunodeficiency disorders	
Lymphoproliferative disorders	Wiskott–Aldrich syndrome
Hodgkin lymphoma	Some acquired immune deficiency syndrome (AIDS)
Non-Hodgkin lymphoma	
Multiple myeloma	Hematological disorders
Chronic lymphocytic leukemia	Some Thalassemia syndromes
	Some sickle cell anemias
Solid tumors	Some congenital neutropenia
Neuroblastoma	Some severe congenital platelet disorders
Bronchial carcinoma	Some Osteopetrosis
Breast carcinoma	
Melanoma	Genetic disorders
Brain tumors	Mucopolysaccharidoses
Osteosarcoma	Leukodystrophies
Ewing's Sarcoma	Other rare metabolic disorders
Teratomas	
Rhabdomyosarcoma	Connective tissue disorders
Others	Some juvenile rheumatoid arthritis
	Some systemic lupus erythematosus

others, in complete hematopoietic engraftment (14). At the present time, almost 75% of all those with severe immune deficiencies can be cured with hematopoietic stem cell transplants and the rate is even higher when a matched sibling donor is available (14).

Selection of patients

Indications for hematopoietic stem cell transplant have, to some extent, changed over the years, particularly related to the curative treatments provided for children with leukemia (Table 2) (22). In the 1980s, the most common indication for a hematopoietic stem cell transplant was salvage therapy for patients with acute lymphocytic leukemia (ALL) who failed to maintain a remission from conventional therapy. However, the likelihood of attaining long-term remission from conventional therapy is now approaching 80%, therefore eliminating the need for a marrow transplant consideration for the vast majority of such children (23). In addition, overall survival rates have also improved for children with lymphoma. Thus, the majority of children with ALL can be cured with conventional approaches and no longer require a transplant. Considering how conventional therapy has increased in intensity over time, it is true that the vast majority of children with ALL and other diseases who require a transplant have already been through a variety of therapeutic protocols and are thus more resistant to the curative effects of the preparative therapy which is provided (Table 3) (24).

Acute myelogenous leukemias

Throughout the 1980s, a number of studies suggested the utility of high dose therapy for patients with acute myelogenous leukemias (25). However, there are now available randomized results from a large-scale study of children with acute non-lymphocytic leukemia undergoing marrow transplantation with a matched sibling donor, compared to those who were treated with conventional chemotherapy because of a lack of a matched sibling donor (25). Very clearly, the long-term survival rates are higher in patients with acute non-lymphocytic leukemia who underwent transplantation with a matched sibling donor. The results from these trials would indicate that those with acute non-lymphocytic leukemia will do much better with a marrow transplant, provided there is a related matched sibling available, than with alternative forms of therapy. The recognition of this phenomena in a biologically randomized study is a key milestone in the development of hematopoietic stem cell transplantation, showing how this disease is quite

Table 3. Remaining stem cell transplant questions in 2002 for children with leukemia

1	What factors best define those to benefit from transplant therapy: (a) initial response; (b) minimal residual disease; (c) biologic markers such as chromosomes; cell morphology, cellular markers or *in vitro/in vivo* growth characteristics; (d) age and/or (e) genetic/pharmacologic profiles.
2	Are all stem cell donors alike in regards to outcome and relapse rates? Matched sibling vs. mismatched family member vs. unrelated adult donors vs umbilical cord derived stem cells.
3	Role of peripheral blood vs. marrow as a source of stem cells.
4	Methods to accelerate immune maturation of stem cell transplants or methods to minimize toxicity to the immune system.

sensitive to the preparative therapy which has been provided early in the course of the disease, as well as the immunologic effects of providing a marrow graft (25).

Neuroblastoma

Of all the solid tumors that occur in the pediatric age group, neuroblastoma has been the most resistant to conventional therapy. However, slow but steady improvement has been made in overall survival (26).

The landmark study in the development of pediatric hematopoietic stem cell transplant was the cooperative group trial which compared transplantation vs. no transplant for those with Stage IV neuroblastoma (27). Previous studies had indicated that allogeneic transplants seemed to provide no evidence for an immunologic effect of the graft itself on the underlying tumor. Fewer problems were associated with high dose therapy and autologous rescue vs. allogeneic stem cell transplant. Thus, the autologous transplant was accepted as a standard therapy for those with neuroblastoma. In fact, the current Children's Oncology Group protocol offers a course of very high dose therapy with stem cell rescue to all patients (27).

One of the major questions that remains to be decided in the next few years is whether there has been an improvement in long-term survival in those with neuroblastoma by the utilization of peripheral stem cells vs. marrow, since marrow runs the risk of contamination with tumor cells. Although most trials of autologous stem cells for transplant purposes utilized a laboratory methodology to purge neuroblastoma cells from the stem cell inoculum, the sensitivity of the assay is such that there may still be quite a number of neuroblastoma cells in the stem cell preparation that is eventually infused into patients (27). Occasionally, patterns of relapse in children following recovery of hematopoiesis suggests that there has been a miliary spread of neuroblastoma cells to a variety of tissues never previously involved with neuroblastoma, and in all likelihood, these tumor cells were contaminating the stem cell inoculum that was infused intravenously (Table 4).

Adding donors

In the late 1970s and early 1980s, a variety of clinical experiments showed the potential of applying high dose chemotherapy with hematopoietic stem cell rescue for an ever-expanding number of children and adults with malignancies, by utilizing allogeneic donors who were less than perfectly matched (28). The first group of donors to be added were those family members who were haploidentical, such as parents or siblings, or in situations where there were more extensive familial investigations to find potentially more closely matched donors (29, 30). Mismatched familial transplants are characterized by one or more major histocompatibility loci differences between donor and recipient, or complete haploidentical transplants, where there is a complete disparity at one of the two HLA A, B or DR loci, and these transplants took place in great numbers in the 1980s and early 1990s (13). Most, but not all, of these clinical protocols attempted to overcome the significant graft-vs.-host disease problems by removing more than two logs of T-lymphocytes from the donor stem cell inoculum (29, 31). From these experiments, the investigators derived a great deal of knowledge and experience in the role of T-lymphocytes when removing them from the transplant inoculum. High rates of rejection and non-engraftment

Table 4. Best approach to treatment of Stage IV neuroblastoma in 2002

1	Diagnostic biopsy with complete resection if possible.
2	Induction chemotherapy—combination—usually 5–6 cycles.
3	Subsequent surgery to resect residual disease.
4	Consolidation therapy—usually high dose chemotherapy and stem cell rescue with marrow or peripheral stem cells, purged of neuroblastoma cells if present.

Table 5. Peripheral stem cells—advantages in adults

1	Easier/less painful to obtain than marrow.
2	Quicker recovery of neutrophils and platelets when used in place of marrow as a source of stem cells
3	No exposure to any anesthetic as would be necessary for collecting marrow stem cells.

suggested either that the process of removing the T-lymphocytes had eliminated extensive numbers of stem cells meant to engraft and produce hematopoietic progeny, or alternatively (28), T-lymphocytes from the donor derived inoculum were important in providing further immune suppression within the host to enable hematopoietic stem cell engraftment. To overcome the latter problem, more preparative therapy was given to some patients but this did not necessarily seem to make a difference. In addition, the removal of T-lymphocytes increased the potential for opportunistic infections due to the subsequent delay in T-lymphocyte recovery, and the delay in T-lymphocyte recovery led to an increased relapse rate in those patients receiving such marrow grafts which were T-lymphocyte depleted. However, the goal of using mismatched or haploidentical donors had achieved an important milestone which was now making it possible for every patient who had a disease that could be treated with hematopoietic stem cell transplant to be eligible for such treatment, without limitations as to whether a donor was available or not (31). The only children who failed to find a donor when considering the use of hematopoietic stem cells from mismatched or haploidentical family donors were those who had been adopted and whose families were not traceable, or alternatively children who had no siblings or parents due to some sort of environmental accident or early death.

Alongside the development of mismatched or haploidentical transplantation was the typing and recruitment of unrelated adult donors. Considering the increased knowledge of the histocompatibility loci and the further delineation of the unique HLA disparities between individuals using molecular techniques, investigations continued on typing large numbers of individuals who volunteered to register with a number of private marrow donor banks and who agreed to be called upon to donate marrow if necessary for an individual who needed a transplant and who had a tissue type similar or identical to that of the potential donor. Reports of these transplants began to appear in the 1980s and some of these were quite successful (30). As expected, most were associated with significant graft-vs.-host disease, either because our preventive treatments for GvHD were inadequate or alternatively, because there had been a lack of appreciation of minor histocompatibility differences between donor and recipient. As an increasing number of allogeneic transplants using unrelated donors developed, there also developed a national interest in bringing together all of these donor banks and setting up a single national registry supplying all allogeneic hematopoietic stem cells for transplant purposes. Thus came the government directive to set up the National Marrow Donor Program and the National Marrow Donor Registry. With increasing recruitment efforts through the 1980s and into the 1990s, well over 4,000,000 donors have been registered world-wide and listed in the NMDP registry, making it possible to find close if not perfect matches more than half the time for individuals without a matched familial donor. Several studies have documented that children will tolerate some histocompatibility difference between donor and recipient, making it possible to find unrelated donors for children with an ever increasing frequency (31). Again, another milestone had been achieved in the development of the pediatric hematopoietic stem cell field by continuing to increase the population of children eligible for transplant by defining new groups of donors, thereby circumventing the earlier problem whereby many patients could not avail themselves of marrow transplant therapy for lack of a matched related allogeneic donor.

Peripheral stem cell transplants

Although experience with syngeneic transplants had yielded the necessary information about circulating peripheral hematopoietic stem cells, to a large extent the application of this technique did not begin until the late 1980s and early 1990s (32–34). Several considerations came about to spearhead this development:

1 Some patients with malignancies undergoing high dose chemotherapy with hematopoietic stem cell reconstitution had previously received irra-

Table 6. Non-myeloablative transplant preparation

1	Reduced preparative therapy and thus potential reduced toxicity
2	Potential to eliminate all radiation.
3	Reduce growth retardation and neuro-psychological effects of full myeloablative therapy.

diation to large marrow spaces or alternatively, had a potential contamination of marrow spaces with tumor cells. Collection of peripheral blood might obviate this problem since there were few if any detectable malignant cells in the peripheral blood and thus collections of stem cells in the peripheral blood would theoretically be less likely to be contaminated with tumor cells.

2 Going to the operating room to obtain hematopoietic stem cells from the marrow space was traumatic and painful, and collections of peripheral blood stem cells could be done as an outpatient in a less painful setting with far less morbidity (33).

As a result, many studies were published on the utilization of peripheral stem cells on how best to collect them and on the timing of collection (32–34). With the development of hematopoietic stem cell cytokines stimulating the production of CD34+ cells, there was now an understanding of how best to improve the yield of collected stem cells. Subsequent studies showed that peripheral stem cells, when given to a host who had undergone ablative chemotherapy or chemotherapy plus radiation, resulted in faster hematopoietic engraftment, fewer hospital days, and potentially improved immune function more quickly than when using hematopoietic stem cells from the marrow space (34). Although similar studies have not been done in children due to the numbers of children available for such studies, in some diseases we have already accepted the utility of obtaining peripheral blood stem cells for transplant purposes (33, 35, 36). However, in many situations in pediatrics, the donors are small children and it therefore becomes more difficult to collect peripheral stem cells from them and more likely that we can obtain an equal or higher total number of hematopoietic stem cells by taking the donor to the operating room and obtaining bone marrow in the traditional manner (33). Thus, even though the use of peripheral stem cells was first documented in pediatric transplants more than 30 years ago, when blood from one twin was infused into another (11), the large scale use of peripheral stem cells, the appreciation of the fact that the stem cells collected from the peripheral blood were somewhat different from those collected from the marrow space, and the extension of this technique to those who have potential marrow involvement with tumor was a whole new era and marked a new milestone in the further development of pediatric hematopoietic stem cell transplantation (Table 5) (32, 33).

Cord blood transplants

In the 1970s, the migration of hematopoietic stem cells from the yolk sack to the liver was understood to the extent that fetal livers were obtained from aborted fetuses and successfully used for transplant purposes (37). Over a period of 10 years, there developed an appreciation of the vast numbers of hematopoietic stem cells in the developing fetus, which at the time of birth is more than 100-fold greater per volume of blood than that found in adults. The sense was that the developing fetus was rapidly growing and needed ever increasing quantities of hematopoietic and immunologic cells. This was translated into an increased number of hematopoietic stem cells, developing in a naive individual and incapable of recognizing and rejecting maternal tissue and probably having little capacity to reject other tissue soon after birth. We knew from hundreds of years of clinical observation that infants were highly susceptible to a wide variety of infectious problems, only because of the lack of immunity at birth and that there was a normal maturation of the immune system in the first 1–2 years of life. In fact, it was well known that children with immune deficiencies did not usually present within the first few months of birth because of the protective levels of cellular and humoral immune factors that are passed from mother to fetus, and that when this protection eventually waned, then the infant's immunodeficiency was exposed (20). With this background in mind, there developed an appreciation of the idea of obtaining umbilical cord blood at the time of birth and using it as a rich source of hematopoietic stem cells which could then be used for transplant purposes (15, 38). Several significant advantages immediately became apparent:

1 With millions of births worldwide, it should be possible to collect umbilical cord blood from every child soon after birth and such blood/cells could be typed and cryopreserved and made available to any individuals with a similar tissue type.

2 Unlike the situation where an adult allogeneic donor needs to be taken to the operating room to obtain marrow or needs to visit a blood bank in order to provide peripheral blood stem cells, the use of these umbilical cord cells entailed no harm to the donor since these blood cells were usually discarded with the placenta at the time of birth.

3 Because the umbilical cord-derived hematopoietic stem cells were naive, it should be possible to use them more readily in situations where there was not a perfect HLA match between donor and

recipient and still see a good hematopoietic engraftment without the lethal complications of graft-vs.-host disease.

In 1988, the first such transplant took place in a child with Fanconi's anemia, receiving hematopoietic stem cells from a previously collected umbilical cord blood specimen from a sibling who was perfectly matched (39, 40). Since that time, a number of umbilical cord blood banks have been set up around the world, some linked by computer and some not, but all dedicated to the business of providing umbilical cord blood for transplant purposes, particularly in situations where there were no available matched sibling donors (15). These transplants have continued in select centers around the world and to date, there still are some problems and difficulties:

1 Umbilical cord-derived hematopoietic stem cells tend to grow a little more slowly, perhaps related to their concentration and numbers following cryopreservation, than freshly obtained peripheral blood stem cells or marrow stem cells from adult donors. The slowness to recovery of blood counts may predispose the transplanted patient to an increased number of infectious problems and complications (38).

2 Although one of the advantages of using hematopoietic stem cells derived from the umbilical cord is their relative naiveté and the potential for a lack of graft-vs.-host disease, there developed a sense in the 1980s and 1990s of the importance of graft-vs.-host disease in providing an immunologic method for controlling the subsequent recurrence of a malignancy following high dose preparative therapy. The absence of such graft-vs.-host disease following the transplant of hematopoietic stem cells derived from umbilical cord predisposes some patients to an increased risk for recurrence of their underlying leukemia (15); and

3 The amount of cord blood obtained in the delivery room is directly related to the experience of the operator. The amount of cord blood collected correlates with the number of stem cells and the number of stem cells in a sample used for transplant purposes correlates with the rate of engraftment. The rate of engraftment and the number of stem cells appears to correlate with ultimate survival (41). Thus, there are many specimens of umbilical cord blood obtained in the delivery room which are low in volume and which are therefore probably not well suited for use in larger children or adults (38).

The availability of umbilical cord blood has once again been a milestone because it has enabled more children who otherwise could not find a suitable donor to have one available. In addition, many children undergoing marrow transplantation need not suffer graft-vs.-host disease and its attendant morbidity/mortality, such as those with genetic diseases or immune deficiencies (40–42). As a result, cord blood has then become an ideal source of hematopoietic stem cells. The first patient transplanted with umbilical cord blood as previously mentioned was a child with Fanconi's anemia, and there had not yet been any evidence of myelodysplasia or leukemic changes (39, 40). As a result, the child would not theoretically benefit from the occurrence of any graft-vs.-host disease and thus the use of umbilical cord blood as a source of hematopoietic stem cells was an ideal source in that particular situation. The overall place of umbilical cord blood in the field of hematopoietic stem cell transplantation remains to be determined, but clearly the advent of this technology and the establishment of numerous umbilical cord blood banks has been a major milestone in the field of pediatric hematopoietic transplantation.

Genetic diseases

For some patients, hematopoietic stem cell transplants are a very crude way of providing new genetic material. It is not selective but rather provides a host of hematopoietic and immunologic stem cells, all of which may bring missing enzymes or missing substrates not present in a child undergoing such a transplant for what is presently defective. Two such examples are noteworthy.

Almost 20 years ago, the first marrow transplant took place in a child with sickle cell anemia (42). Sickle cell anemia is an inherited genetic disorder characterized by abnormal hematopoiesis, deformities and increased sickling of red cells secondary to abnormal hemoglobin synthesis and an associated array of clinical difficulties. The replacement of these abnormal hematopoietic stem cells with new ones making cells with normal hemoglobin eliminates future problems associated with the disease for the child undergoing such a transplant (43). In fact, hematopoietic transplants have been curative (40). The problem is related primarily to the selection of patients: when to offer the transplants to patients and when too much damage may have been done by the underlying disease to warrant proceeding with the transplants. Since the vast majority of children with sickle cell disease make it into adult life, families have a very difficult time

making a decision to proceed with a marrow transplant when there might be as high as a 15–30% significant morbidity and mortality associated with the procedure (44, 45).

A number of mucopolysaccharide disorders, as an example of another genetic disorder, have been cured with a hematopoietic stem cell transplant (46). In these cases, there is a missing enzyme which can be found within neutrophils and other cells originating from the bone marrow space, and these new cells will replace the missing enzyme and deal with substrates which accumulate in abnormal places where such accumulation may result in significant damage. In most of the mucopolysaccharide disorders, proteins accumulate in the nervous system as well as in the heart and liver and eventually lead to the dysfunction of these organs and death. A marrow transplant provides enzymes which are missing to help degrade and deal with the substrate which accumulates. Damage previously associated with the abnormal condition may not be repaired over time but in general, one is looking to halt the progression of the underlying disease.

Significant progress has been made in learning for which diseases it is best to offer such transplants, the appropriate timing, and the limitation of the procedures in other patients in terms of correcting or halting the further progression of the underlying illness.

Non-myeloablative transplants

It has been well known for some time that one of the beneficial aspects of an allogeneic stem cell transplant has been the immunologic surveillance and immunologic treatment which is brought about by the growth of a new immune system. Patients experience graft-vs.-host disease with variable frequency and graft-vs.-host disease has been shown in several studies to be helpful if not essential in preventing the recurrence of an underlying malignancy. There appears to be a graft-vs.-tumor or graft-vs.-leukemia effect from the new source of allogeneic hematopoietic stem cells (47, 48).

This fact was further emphasized by studies using delayed lymphocyte infusions (DLI) to treat recurrent disease, as well as to treat significant viral infections which occur post-transplantation (47–49). Considering the delay in the recovery of normal T-lymphocytes following an allograft, lymphocytes can be obtained from living hematopoietic stem cell donors and these cells can be utilized for treatment, either to prevent recurrent diseases by prophylactic infusions of such lymphocytes or to treat the recurrent chronic myelogenous leukemia which may occur following a transplant.

Considering the immunologic effects of the graft, and animal work which showed that with minimal conditioning therapy and minimal establishment of an allograft within the bone marrow space, further immune suppression from donor lymphocytes would effectively create complete chimerism and full engraftment, thereby providing individuals with the benefit of the new immune system provided with the new allograft (50). This approach holds great promise in establishing the presence of a new allograft and as such is really the goal of the transplant process and at the same time, limit the preparative therapy given, since a complete establishment of hematopoiesis is not initially necessary but will be effected by subsequent infusions of lymphocytes. This has been one of the milestones in the development of pediatric hematopoietic stem cell transplantation. Those with an enzyme disorder, and potentially those with disorders only characterized by missing cellular function, need a small proportion of hematopoietic stem cells to fully engraft and function to correct the underlying defect (50). A recent patient reported with Chédiak Higashi syndrome is a good example whereby only a small proportion of the neutrophils are actually of donor origin and therefore normal, but the actual number is high enough to have prevented any significant infections occurring in the years following the establishment of the allograft (51).

The use of these non-myeloablative transplants, meaning that the preparative therapy has been limited in extent and toxicity, has permitted a very small proportion of donor cells to engraft, but these cells are then engineered to become fully chimeric with the recipient by the use of DLI to further suppress the host. These types of transplants, whereby the preparative therapy is minimized, are undergoing trials in the elderly and in more fragile individuals who would otherwise not qualify for transplant, in the hope that they will receive the beneficial effects of a new immune system and the immunologic surveillance thus provided, without the toxicity which often is associated with the preparative therapy given to bring about full engraftment. In addition, there are children with disorders that would potentially be made worse with full doses of preparative therapy, including total body irradiation. Thus a non-myeloablative transplant limits the amount and type of preparative therapy given, thereby limiting the potential toxicity to

the patient. Limiting the preparative therapy reduces the long-term effects but still permits full eventual engraftment and provision of the missing components of the immune system or immune surveillance (Table 6).

Conclusions

When hematopoietic stem cell transplants began almost 50 years ago, they were a shot in the dark to try and correct underlying significant diseases and were eventually utilized to correct immune deficiencies. Over the ensuing 40 years, a variety of newer techniques were developed to perfect the source of stem cells and increase our understanding of clinical situations in which one source of stem cells might be better than another (52, 53). Improvements in supportive care made it possible for an ever increasing number of children to survive the effects of the preparative therapy and the subsequent graft-vs.-host disease and immaturity of the immune system. High dose therapy with hematopoietic stem cell rescue has become a mainstay of modern therapy for children with Stage IV neuroblastoma and a significant salvage therapy for patients with a variety of other diseases when these children have failed to respond to more conventional approaches. The approaching frontier involves the *in utero* identification of genetic defects and immunodeficiency diseases, thereby utilizing *in utero*-administered hematopoietic stem cells to provide definitive curative therapy (54, 55). Although children with leukemia make up an ever decreasing number of those eligible for transplantation because of the success of the initial therapeutic non-transplant treatment they receive (22), there still are a number of children benefiting from transplantation who have been treated rather heavily with alternative therapy and we know that there are a variety of diseases that now benefit from replacement of the marrow graft and provision of a new immune system and improved immune surveillance.

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Related Articles, Links

Automated isolation of mononuclear cells using the Fenwal CS3000 blood cell separator.

Areman EM, Cullis H, Sacher RA, Cottler-Fox M, Deeg HJ.

Division of Transfusion Medicine and Bone Marrow Transplantation, Georgetown University Hospital, Washington, D.C.

We describe a method for in vitro isolation of mononuclear cells from peripheral blood or bone marrow using a Fenwal CS3000 Apheresis device without employing density gradients or sedimenting agents. The automatic processing program requires minimal operator intervention and no subjective operator decisions. A mean of 67% of starting mononuclear cells were recovered in a 100 ml product having 95% mononuclear cells and less than 1% of the original red blood cells. The average processing time was 35 minutes.

PMID: 2308992 [PubMed - indexed for MEDLINE]

1: Haematologica. 1990 Jan-Feb;75 Suppl 1:43-7.

Related Articles, Links

haematologica

Human bone marrow processing using Cobe 2991 and CS 3000 blood cell separators for further ex vivo manipulation.

Angelini A, Dragani A, Iacone A, D'Antonio D, Accorsi P, Quaglietta AM, Berardi A, Fioritoni G, Di Bartolomeo P, D'Emilio G, et al.

Divisione di Ematologia e Centro Trasfusionale, Ospeda-le Civile, Pescara, Italy.

Several automated procedures are now available to enrich stem cells from large bone marrow (BM) volumes prior to ex vivo treatment or cryopreservation. This report details our experience using a ficoll-hypaque (F/H) gradient on Cobe 2991 cell washer and a CS 3000 continuous flow separator, on 90 BM processed for allogeneic and autologous transplantation. In the Cobe series, from 70 BM aspirates, 89 +/- 5% of the original mononuclear cells (MNC) was found in the light density fraction with a erythrocytes (RBC) and granulocytes (PMN) removal of 98 +/- 1 and 97 +/- 4.5%, respectively. Over 80% of the initial myeloid precursors (CFU-GM) were recovered in a small final volume. Twenty BM processing were performed with a CS 3000 separator using program "3" and granulo chamber. This technique yielded 86 +/- 9% of the initial MNC while 85 +/- 10% of RBC and 90 +/- 1.1% of PMN was removed. Over 75% of the original CFU-GM was recovered in the final product. Both techniques are effective to large-scale purification of progenitor cells and readily available as routine procedures for marrow processing.

PMID: 2351343 [PubMed - indexed for MEDLINE]

1: J Hematother. 1992 Winter;1(4):349-59. Related Articles, Links

Use of the Terumo SteriCell for the processing of bone marrow and peripheral blood stem cells.

Janssen WE, Lee C, Smilee R, Carter R.

University of South Florida, Department of Internal Medicine, Tampa.

The SteriCell cell processing instrument is a good choice for a stem cell processing laboratory that is of sufficient size that they cannot share an apheresis machine with the blood bank. It is a laboratory instrument, with no facility for patient connection. Because of its minimal size and weight, it is easily stored in a cramped laboratory. Its automated programs are appropriate for processing of bone marrow and peripheral blood stem cells, and it is quite easy to learn how to use (in our laboratory, most individuals have been completely facile with the SteriCell after fewer than six processings). Based on reported results from other instruments, the SteriCell provides cell yields that are comparable to competing instruments. Service (provided by Haemonetics) has been satisfactory, and support from Terumo has been excellent. We can recommend this instrument to any other laboratory.

PMID: 1345677 [PubMed - indexed for MEDLINE]

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: James P. Elia	)	
SERIAL NO.: 09/836,750	)	EXAMINER: E.C. Kemmerer, Ph.D.
FILED: April 17, 2001	)	GROUP ART UNIT: 1646
FOR: METHOD FOR GROWING MUSCLE IN A HUMAN HEART	)	

THIRD SUPPLEMENTAL DECLARATION
<u>OF RICHARD HEUSER, M.D., F.A.C.C., F.A.C.P.</u>

I, Richard Heuser, declare as follows:

1. I have offices at 500 West Thomas Road, Suite 900, Phoenix, Arizona 85013.

2. This Third Supplemental Declaration is submitted in addition to my previous Declaration, dated June 5, 2003; my Supplemental Declaration dated February 4, 2004; and my Second Supplemental Declaration dated July 18, 2004. No changes are made to any of such previous Declarations.

3. My Curriculum Vitae is attached as Exhibit A to my Declaration of June 5, 2003.

4. It is my understanding that the Examiner in charge of the above-identified patent application is also in the Examiner in charge of co-pending patent application Serial No. 09/794,456. In an Advisory Action dated November 26, 2004, for aforesaid Serial No. 09/794456, the Examiner further questioned my qualification to render my opinions in the three previous Declarations mentioned in above Paragraph 2. It is my further

understanding that the Examiner reviewed my U.S. Patent No. 6,190,379 and did not find mention of delivery of any substance to the myocardium nor the word "cell." Also, the Examiner questioned my role in the cell delivery portion of Bioheart's laboratory and clinical trials using skeletal muscle cultured and modified. I provide the following information to respond to the Examiner's newly raised questions.

5. Regarding, U.S. Patent No. 6,190,379, the following is stated in my Second Supplemental Declaration:

> In my U.S. Patent No. 6,190,379 entitled "Hot Tip Catheter," I developed a technique to deliver radiofrequency (PMR). In the full embodiment of the patent, I discuss delivery of protein and/or muscle cells in the myocardium using the inventive technique.

By the above statement, I meant that the device shown in the patent has been used for the delivery of protein and/or muscle cells to the myocardium. At a presentation at the Angiogenesis Meeting in 1999 in Washington, D.C., we described this use of growth factors in a pig model with the development of neo vascularization. Moreover, I have had discussions with Bioheart regarding the use of my U.S. Patent No. 6,190,379 for delivery of cells.

Regarding my work at Bioheart, the following is stated in my Second Supplemental Declaration:

> I have been involved as a member of the scientific advisory board with the world leader in cardiomyocyte regeneration, Bioheart, Miami Lakes, Florida. This company has been involved with laboratory and clinical trials using skeletal muscle cultured and modified. The sample is then delivered into the myocardium via a surgical or catheter approach.

To provide further information regarding the Examiner's questioning my involvement with Bioheart, I am a Scientific Advisory Board Member and in such role advise Bioheart throughout its pre-clinical and clinical work involving the delivery of skeletal muscle

cells into the myocardium. I am also an investigator with Bioheart's Phase 3 clinical trials in the United States. Such trials have not yet commenced.

6. Declarant states that the above opinion was reached independently.

Declarant understands that (1) any willful false statements and the like made herein are punishable by fine or imprisonment, or both (18 U.S.C. 1001) and may jeopardize the validity of the application or any patent issuing thereon, and (2) that all statements made of Declarant's own knowledge are true and that all statements made on information and belief are believed to be true.

Further Declarant sayeth not.

Date: 2/15/05

Richard Heuser, M.D., F.A.C.C., F.A.C.P.

NATIONAL CANCER INSTITUTE

Cancer Facts

NCI Home
CIS Home
Dictionary

Date reviewed: 08/08/2000
Editorial changes made: 05/06/2002

Soft Tissue Sarcomas: Questions and Answers

1. **What is soft tissue?**

   The term *soft tissue* refers to tissues that connect, support, or surround other structures and organs of the body. Soft tissue includes muscles, tendons (bands of fiber that connect muscles to bones), fibrous tissues, fat, blood vessels, nerves, and synovial tissues (tissues around joints).

2. **What are soft tissue sarcomas?**

   Malignant (cancerous) tumors that develop in soft tissue are called sarcomas, a term that comes from a Greek word meaning "fleshy growth." There are many different kinds of soft tissue sarcomas. They are grouped together because they share certain microscopic characteristics, produce similar symptoms, and are generally treated in similar ways. (Bone tumors [osteosarcomas] are also called sarcomas, but are in a separate category because they have different clinical and microscopic characteristics and are treated differently.)

   Sarcomas can invade surrounding tissue and can metastasize (spread) to other organs of the body, forming secondary tumors. The cells of secondary tumors are similar to those of the primary (original) cancer. Secondary tumors are referred to as "metastatic soft tissue sarcoma" because they are part of the same cancer and are not a new disease.

   Some tumors of the soft tissue are benign (noncancerous). These tumors do not spread and are rarely life-threatening. However, benign tumors can crowd nearby organs and cause symptoms or interfere with normal body functions.

3. **What are the possible causes of soft tissue sarcomas?**

   Scientists do not fully understand why some people develop sarcomas while the vast majority do not. However, by identifying common characteristics in groups with unusually high occurrence rates, researchers have been able to single out some factors that may play a role in causing soft tissue sarcomas.